Archives of Internal Medicine

VOLUME 49 MARCH, 1932 NUMBER 3

THE NORMAL RANGE OF GASTRIC ACIDITY FROM YOUTH TO OLD AGE

AN ANALYSIS OF 3,746 RECORDS*

FRANCES R. VANZANT, M.D.†

WALTER C. ALVAREZ, M.D.

GEORGE B. EUSTERMAN, M.D.

HALBERT L. DUNN, M.D.

AND

JOSEPH BERKSON, M.D.

ROCHESTER, MINN.

At first glance it would seem inconceivable that for sixty years physicians could have gone on studying gastric acidity in the sick, without, somewhere along the way, pausing to secure standards of normal. There are two explanations for this peculiar behavior of the medical profession: one, that we have always been more ready to study disease and to treat it than to make the basic anthropologic and statistical studies that would enable us to say where normal ends and disease begins; and the other, that it is not easy to get several thousand normal persons to submit to gastric intubation.

Much work has been done with medical students and with infants, but, unfortunately, most of the published reports of these studies are useless for statistical analysis because distribution tables were not supplied, and measurements from several age groups were averaged together.

Although the literature on gastric analysis is enormous, we have been able to find only a few papers that throw light on the way in which the acidity of the gastric contents varies from youth to old age. The best of these is by Polland and Bloomfield,[1] who studied 90 patients recovering from injuries or diseases other than gastro-intestinal. They used histamine as the stimulus to gastric secretion, and found what appear to be straight line (inverse) relations between the amount and the acidity of the secretion and age. Obviously the group studied is too

* Submitted for publication, May 25, 1931.

* Read before the Gastro-Enterological Association, Atlantic City, May 4, 1931.

† Fellow in Medicine, the Josiah Macy, Jr., Foundation, on duty in the Mayo Foundation.

1. Polland, W. S., and Bloomfield, A. L.: Normal Standards of Gastric Function, J. Clin. Investigation **9**:651 (Feb.) 1931.

small for a detailed analysis of the problem, but this need not lessen the gratitude of the medical profession to the authors for the excellent start that they have made. Valuable data on the influence of age, sex and physical fitness on the incidence of achlorhydria are to be found in an article by Bloomfield and Keefer.[2]

To those who may now be asking "But why bother so about standards of normal?" our answer is: "Why bother about standards of normal for basal metabolism or for any other measurable function of the body?" Here, let us say, is a woman of 50 years with achlorhydria; is it a disease about which we should become anxious, or is it a symptomless peculiarity of every fourth normal person of that age? A few months ago, when we began this study, we could not have given an answer to this question; today, we think we can.

TYPE OF CASE USED IN THE PRESENT STUDY

It occurred to us that every year in a large institution like the Mayo Clinic hundreds of practically normal persons submit to gastric analysis because they have a few symptoms suggestive of cholecystitis, pernicious anemia, migraine or ulcer. In many cases, probably, if the physician who first saw the patient had taken a more careful history, he would have recognized the functional nature of the few digestive disturbances and would not have bothered to order a gastric analysis.

Accordingly, one of us (Dr. Vanzant) reviewed 16,000 records of patients (registered in the years 1928 to 1931) who submitted to gastric analysis, picking out for special study 3,381 (as will be explained later, 365 additional cases were reviewed from the literature) in which the absence of symptoms suggesting serious disease and the inability of the medical examiner and the roentgenologist to show anything wrong with the stomach, duodenum, gallbladder or colon seemed to justify the diagnosis of a normal digestive tract. Furthermore, all cases were excluded in which the patient was accustomed to the use of alcohol or in which there was serious disease such as syphilis, advanced cardiovascular-renal incompetency, anemia, leukemia, jaundice, thyrotoxicosis, myxedema, infectious arthritis, tuberculosis, Addison's disease, infestation with intestinal parasites, diarrhea, disease of the liver or pancreas or appendicitis. In addition, all cases were excluded in which there was severe malnutrition or in which the patient was recovering from serious illness of any kind.

The diagnoses made in most of the accepted cases were: fatigue, or anxiety neurosis, migraine, constipation, negative findings, irritable bowel or mucous colitis. In many cases an analysis of gastric secretion

2. Bloomfield, A. L., and Keefer, C. S.: Gastric Acidity: Relation to Various Factors Such as Age and Physical Fitness, J. Clin. Investigation **5**:285 (Feb.) 1928.

was made because the patient complained of the occasional presence of paresthesia, sore tongue, abdominal pain or tenderness, bad breath or belching.

HOMOGENEITY OF THE DATA

After our study was almost completed we reviewed the data and picked out a large group of cases in which it seemed as if there could be no question about the normalcy of the person studied; we compared the distribution polygons of this group with the ones that we had already obtained and found them to be almost identical. This discovery greatly encouraged us in our belief that we have succeeded in obtaining data from fairly normal persons.

It was easy to find enough patients within the range of middle age, and we stopped collecting them as soon as we had enough to give smooth distribution curves such as are presented in chart 1. After that, many thousands of records had to be searched before we could find a sufficient number of apparently healthy old men and women with few symptoms and negative findings.

We found so few persons with ages less than 20 years that a satisfactory statistical analysis of their measurements could not be made. We, therefore, searched the literature [3] for gastric analyses made on presumably normal children and youths, and were able to find 365; 203 of these persons were girls and 162, boys. In all cases the test meal used was of the Ewald type. We used the data thus obtained to fill the gap in our material.

TECHNIC OF GASTRIC ANALYSIS

The test meal used at the Mayo Clinic consists of eight arrowroot cookies and 400 cc. of water. After one hour a sample of the gastric contents is removed with the Sawyer tube; it is tested for free acid, and if this is present the stomach is emptied and the tube is withdrawn. If, however, there is no free acid, the tube is left in and three more samples are removed at intervals of fifteen minutes. The results of titration are expressed in the usual terms of cubic centimeters of tenth-normal sodium hydroxide required to neutralize 100 cc. of gastric juice.

For the purposes of this paper we have in every case used the figures for total and free acid obtained at the end of the first hour. The only use made of subsequent readings with the fractional test was to help us in distinguishing between true

3. Jacobsen, A. T. B.: Some Investigations Concerning the Gastric Secretion in Children of 1 to 4 Years Suffering from Diseases of the Stomach and Intestines, Together with Some Remarks as to Treatment, Acta med. Scandinav. **52**:773, 1920. Klementsson, Emil: Recherches sur le suc gastrique chez les enfants de 1 à 12 ans, Acta pædiat. **3**:136, 1923. Muhl, Greta: The Secretion of Hydrochloric Acid in Normal Conditions and in Chronic Gastric Affections of Children from 1 to 13 Years of Age, Acta pædiat. **4**:356, 1925. Wright, C. B.: Gastric Secretion, Gastro-Intestinal Motility and Position of the Stomach in a Group of 250 Children of the Lymanhurst School, Arch. Int. Med. **33**:435 (April) 1924.

and false achlorhydria. All data from persons who did not show free acid at the end of the first hour have been segregated into a group which is represented by the lines corresponding to abscissa zero in chart 1, and by the small polygons in chart 2.

INCIDENCE OF ACHLORHYDRIA

The first thing that struck us when we arranged our data in the form of percentage distribution tables and polygons (table 1 and chart 3) was the remarkably high incidence of achlorhydria and the steady increase of this incidence with age.

In table 1 all cases in which free acid was not obtained on the first aspiration at the end of an hour are listed under the heading of apparent

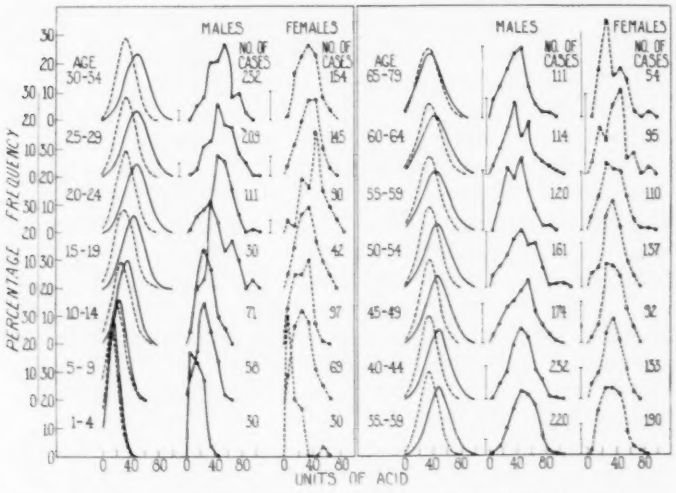

Chart 1.—The polygons represent the frequency with which free hydrochloric acid of different concentrations was found in males and females at different ages. For convenience of spacing on the page, the polygons representing data from older subjects have been placed to the right instead of above those representing data from the younger subjects. In both halves of the figure the polygons in the second and third columns represent the actual data. The first column represents these polygons smoothed. The vertical lines drawn to the left of a number of polygons in the second and third columns represent the percentages in the group of subjects with achlorhydria.

achlorhydria. If free acid did not appear either on repeated fractional analysis or after the injection of histamine, the patient was considered to have what for convenience we will call true achlorhydria. Unfortunately the control study with histamine was made in only a small percentage of the cases. It will be noted that in most of the cases in which free acid was absent at the first aspiration, it remained absent in subsequent samples.

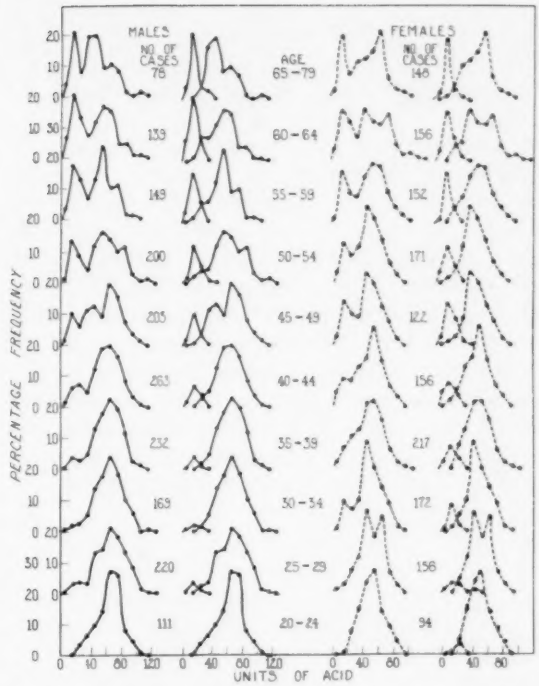

Chart 2.—The polygons in the first and third columns represent the frequency with which total acidity of different concentrations was found in men and women at different ages. The bimodal nature of the polygons suggested the presence of two groups of persons, one with and the other without free acid, and in the second and fourth columns the distributions of data from these two groups are shown separately.

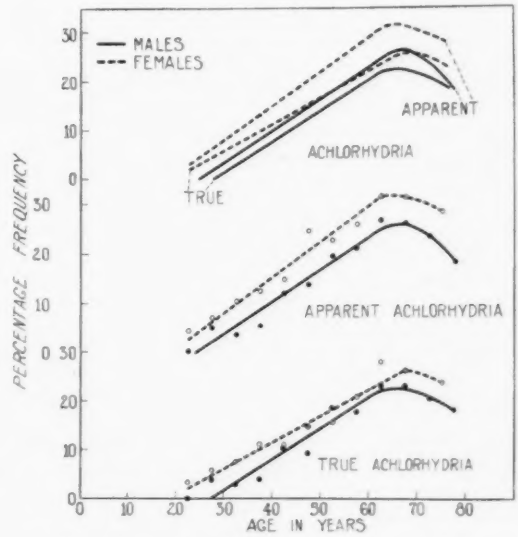

Chart 3.—The curves show the relation between the incidence of achlorhydria and age.

It should be noted that we have carefully avoided the use of the term "achylia" which we think should probably be used only in those cases in which the stomach is dry and in which repeated injections of histamine fail to produce any secretion. We doubt even if there is any real difference between what we have called true and probable achlorhydria. In both there is some secretion of acid and the only difference is that some of it is more deeply submerged by the neutralizing fluid.

Chart 3 shows that for both true and apparent achlorhydria there is from youth to about the age of 65 years in both sexes a straight-line correlation between the incidence of the defect and age. After the age of 65 years there appears to be a definite falling off in the amount of achlorhydria, possibly because the persons with achlorhydria are not so hardy or long-lived as are those who have a strongly acid gastric juice.

TABLE 1.—*Achlorhydria*

	Males					Females				
	Apparent Achlorhydria		True Achlorhydria			Apparent Achlorhydria		True Achlorhydria		
Age, Years	Cases	Per Cent	Cases	Per Cent	Total Cases	Cases	Per Cent	Cases	Per Cent	Total Cases
20–24	..	....	..	....	111	4	4.3	3	3.2	94
25–29	11	4.9	8	3.6	220	11	7.0	9	5.8	156
30–34	6	3.5	5	3.0	169	18	10.4	13	7.6	172
35–39	12	5.2	9	3.9	232	27	12.4	24	11.1	217
40–44	31	11.8	27	10.3	263	23	14.9	17	10.9	156
45–49	29	13.7	19	9.3	203	30	24.6	18	14.8	122
50–54	39	19.5	37	18.5	200	34	22.8	27	15.8	171
55–59	32	21.2	27	17.8	152	39	26.2	31	20.8	149
60–64	42	26.9	36	23.1	156	44	31.6	39	28.1	139
65–69	27	26.2	24	23.0	103	18	31.6	15	26.3	57
70–74	8	23.5	7	20.6	34	6	28.6	5	23.8	31
75–79	2	18.2	2	18.2	11					
Total	239	12.9	200	10.8	1,854	254	17.4	201	13.8	1,454

It is curious also that at all ages the women show a greater tendency to achlorhydria (about 3 per cent on the scale) than do the men. Strange to say, in our series of cases at the Mayo Clinic there was no instance of true achlorhydria in the 111 men aged from 20 to 25 years. In women the incidence of true achlorhydria varied from 3 per cent at the age of 20 years to 28 per cent at the age of 60 years. In men the highest percentage of achlorhydria was 23 at the age of 60 years.

INCIDENCE OF ACHLORHYDRIA AS OBSERVED BY OTHERS

Kelling[4] found free acid absent in 15 per cent of 2,031 men and in 19 per cent of 1,116 women examined. He took care to exclude only the organic gastric and duodenal diseases and he did not segregate his

4. Kelling, G.: Statistisches über Salzsäuremangel im Magen, Arch. f. Verdauungskr. **15**:568, 1909.

cases according to age. Conner,[5] at the Mayo Clinic, found achlorhydria in 14.6 per cent of 691 men and in 20.4 per cent of 509 women of all ages. He took a consecutive series of reports from the laboratory in which gastric analyses are made and did not attempt to exclude cases of serious organic disease. With a smaller group of cases in England, Bell[6] obtained figures of 13.8 per cent for men and 16.1 per cent for women. Bennett and Ryle[7] found achlorhydria in 4 of 100 apparently healthy students. A similar figure has been obtained by a number of investigators who have studied young men and women.

Muhl did not find a single case of achlorhydria in 40 normal children, and Klumpp and Neale[8] were also unable to find any instance of this abnormality in 80 children studied. Wright, however, found 4 per cent of 230 apparently normal children to be without free hydrochloric acid.

Conditions are different in the aged; Seidelin[9] found free acid absent or very low in 40 per cent of aged persons. He studied Danish people of the working classes, aged more than 50 years. Dedichen[10] found anacidity in 66 of 99 apparently healthy men and women in an old people's home in Copenhagen. Davies and James,[11] with the usual test meal and fractional analysis, failed to find free acid in 32 of 100 normal persons aged more than 60 years. With histamine, they obtained acid in 13 of the 32.

The fact that our figures are lower than those published by other observers leads us to hope that we have been more successful in excluding cases in which the abnormality was due to disease. It may be, however, that the incidence of achlorhydria varies with different races and in different climes.

NORMAL RANGE OF FREE ACID IN MEN AND WOMEN

The data on which this study is based are presented in table 2 and chart 1. There it will be seen that after the earlier years of life the

5. Conner, H. M.: Hereditary Aspect of Achlorhydria in Pernicious Anemia; Study of Gastric Acidity in 154 Relatives of 109 Patients Having Pernicious Anemia, J. A. M. A. **99**:606 (March 1) 1930.

6. Bell, J. R.: Notes on a Consecutive Series of 425 Gastric Analyses by the Fractional Method, Guy's Hosp. Rep. **72**:302 (July) 1922.

7. Bennett, T. I., and Ryle, J. A.: Studies in Gastric Secretion: V. A Study of Normal Gastric Function, Based on One Hundred Healthy Men by Means of the Fractional Method of Gastric Analysis, Guy's Hosp. Rep. **71**:286, 1921.

8. Klumpp, T. G., and Neale, A. V.: The Gastric and Duodenal Contents of Normal Infants and Children, Am. J. Dis. Child. **40**:1215 (Dec.) 1930.

9. Seidelin, quoted by Faber.

10. Dedichen, Lucien: Anacidity in Old Persons, Acta med. Scandinav. (supp.) **7**:345, 1924.

11. Davies, D. T., and James, T. G. I.: An Investigation into the Gastric Secretion of a Hundred Normal Persons Over the Age of Sixty, Quart. J. Med. **23**:1 (Oct.) 1930.

TABLE 2.—*Free Acid*

Group	Units of Acid	Males: Age, Years 1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-79	Total	Females: Age, Years 1-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-79	Total
No free acid.....	0	1	2	..	..	..	11	6	12	31	29	39	32	42	37	242	4	2	..	2	4	11	18	27	23	30	34	39	44	24	262
With free acid...	1- 9	11	5	3	..	1	1	..	2	1	5	7	..	3	7	46	18	6	12	2	2	5	2	3	7	2	6	5	4	..	74
	10- 19	10	10	14	..	6	5	8	6	13	12	12	11	10	12	129	6	18	24	6	17	16	25	30	12	6	9	13	15	9	206
	20- 29	8	20	24	1	9	22	13	21	22	22	18	26	18	19	243	5	22	24	11	14	28	34	45	31	26	34	26	11	19	330
	30- 39	1	14	19	9	12	26	33	36	44	26	27	22	29	25	323	..	19	29	10	32	39	41	45	38	25	42	24	23	8	375
	40- 49	..	8	7	7	30	53	34	50	58	32	32	31	15	27	384	..	4	7	7	13	39	35	41	28	17	29	23	28	9	280
	50- 59	..	1	4	4	28	38	43	47	51	39	24	17	21	12	329	1	..	1	4	8	14	12	17	14	11	12	13	5	7	119
	60- 69	..	..	..	5	17	36	13	39	24	20	25	9	8	5	201	..	..	..	2	4	4	5	6	3	5	5	4	7	1	46
	70- 79	..	..	..	3	7	17	15	15	16	12	11	2	5	2	105	..	..	..	..	..	..	..	3	..	..	..	..	1	..	..	4
	80- 89	..	..	..	..	..	10	4	3	2	5	1	2	3	2	32	..	..	..	..	..	..	..	..	..	..	..	..	1	2	1	4
	90- 99	..	..	..	1	1	1	..	1	1	1	2	..	1	..	9	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	100-109	..	..	..	..	..	..	..	..	..	..	2	..	1	..	3	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
	Total	30	58	71	30	111	209	163	220	232	174	161	120	114	111	1,804	30	69	97	42	90	145	154	190	133	92	137	110	95	54	1,438
Median.....		14.0	22.0	22.7	47.0	49.0	49.5	48.4	49.0	46.2	46.9	45.0	40.3	39.0	36.6		8.3	24.8	25.2	33.0	33.8	36.2	33.9	33.8	34.3	35.0	34.6	34.6	37.6	29.5	
Mode.....		12.7	11.5	26.1	39.6	50.5	47.3	49.4	49.5	46.4	42.2	44.3	40.6	32.6	36.2		0.9	25.1	30.2	29.4	33.0	38.0	33.8	32.3	34.6	32.8	35.3	33.3	39.4	20.7	
Mean.....		14.7	27.2	28.5	50.7	48.2	50.6	47.9	48.8	46.3	49.3	45.4	40.2	42.2	36.8		12.0	24.6	22.7	32.1	33.6	35.3	34.0	34.5	34.2	36.1	34.9	35.3	36.7	33.9	
Probable error of mean		1.1	1.1	1.0	2.0	1.0	0.8	0.9	0.7	0.7	0.9	1.1	1.0	1.2	1.1		1.2	0.9	0.9	1.6	1.0	0.8	0.7	0.7	0.8	1.0	0.8	1.1	1.2	1.4	
Standard deviation.....		8.7	11.8	12.1	16.2	16.2	17.5	16.4	16.3	16.2	16.7	20.5	15.8	19.6	17.5		9.4	10.5	13.2	14.9	13.8	13.6	13.5	14.2	13.8	13.7	13.4	16.2	16.7	15.3	
Probable error of standard deviation.....		0.8	0.7	0.7	1.4	0.7	0.6	0.6	0.5	0.5	0.6	0.8	0.7	0.9	0.8		0.8	0.6	0.6	0.7	0.7	0.5	0.5	0.5	0.6	0.7	0.6	0.7	0.8	1.0	
Coefficient of variability		59.3	43.3	42.4	32.0	33.5	34.5	34.2	33.5	35.0	33.8	45.6	39.3	46.4	47.5		78.2	42.8	58.1	46.3	41.0	38.6	39.6	41.2	40.4	38.0	38.5	45.9	45.6	45.0	

distributions become more and more bimodal owing to the existence of two types of human beings, one with free acid and the other without. That these groups are distinct is shown also by the bimodality of the distribution polygons representing total acidity (chart 2).

For a number of reasons it seemed best to make two different distribution polygons for the two groups of data. In the first place, it did not seem to be good statistical practice to group all the figures from achlorhydric persons opposite the one abscissa of zero because the stomachs of these persons secrete varying amounts of acid although it is more or less deeply submerged by the diluting fluid, even though it does not appear as free acidity. Furthermore, with the data from all (apparently and actually) achlorhydric persons excluded, we were left with fairly symmetrical and typically shaped distribution curves which lent themselves easily to smoothing and to other forms of mathematical treatment.

It should be noted that in chart 1 the first four polygons (ages from 1 to 20 years) represent mainly data secured from the literature. The other polygons represent data collected at the Mayo Clinic. The first series shows smoother curves representing, for men and women, percentage distribution of the figures as they probably would appear if a sufficiently large number of observations had been available for study. To get these curves, the means and standard deviations of the data obtained from patients with free acid were plotted as in chart 4. Curves were then fitted through the points to represent the most probable location of means and standard deviations. With these corrected or smoothed values as a basis, "normal," "cocked hat" curves were then drawn. In most instances they closely followed the actual data.

The second and third columns in chart 1 show for men and women, respectively, the actual percentage distributions of acid values at different ages. The length of the line drawn to the left of each polygon represents the percentage of cases of apparent achlorhydria in each of the age groups. The polygon represents the percentage distribution of the cases that were left after the achlorhydric ones were removed. In them, the sum of the ordinates is 100.

The first set of polygons shows, first, that the free acid of the stomach increases rapidly through childhood and up to the age of 15 years. Careful mathematical treatment of the measurements made on young persons indicate that there is an inflection of the line such as is shown in the chart representing mean acidities (chart 4). After this time there appears to be no definite change of the mode in women until the age of 65 years, and in men until the age of 45 years. About the age of puberty the modal value for boys begins to rise above that for

girls, and by the age of 25 years there is a difference of about 12 points. This difference begins to diminish at the age of 40 years owing to a decrease in the modal value for men.

The theoretical modes were located by two methods which were found to check fairly closely. In one method we used Pearson's empiric formula which relates the mode to the mean and the median, and in the other we determined the distance from mean to mode by multiplying the index of skewness by the standard deviation.

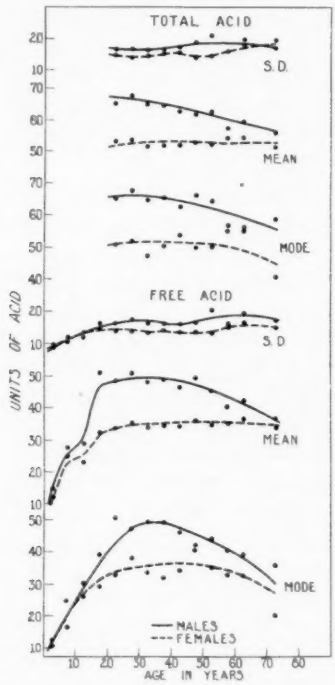

Chart 4.—The curves show the means, calculated modes and standard deviations for free and total hydrochloric acid in males and females at different ages.

The changes in the modes for men and women are shown more clearly in chart 4, where it will be seen that the modal free acidity in men decreases steadily after the age of 40 years. We cannot be sure that it falls off in women because there were only 54 women in the group aged 65 years or more. If we were to discard this one datum a straight line could be drawn in chart 4 just as it can be drawn through the data representing the mean free acidity (in women) from youth to old age.

The sameness of free acidity in old men and women can be seen also from the fact that the two smoothed curves at the top of the first column in the second half of chart 1 are almost identical and closely overlapping.

A study of the polygons in chart 1 shows a slight widening for men after the age of 50 years and for women after the age of 55 years. This is shown again graphically in the curves representing standard deviation

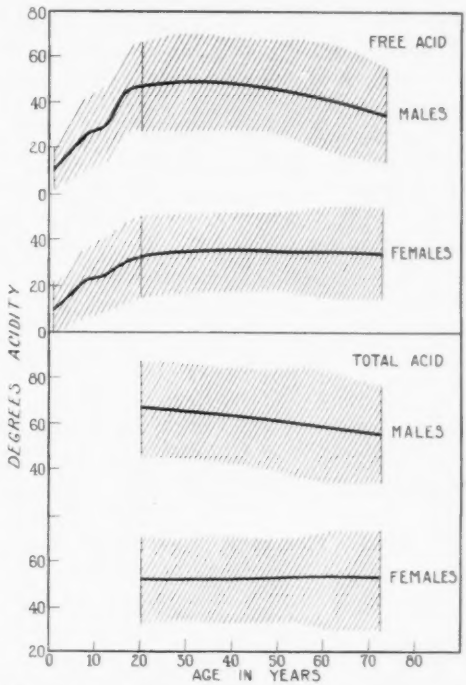

Chart 5.—Standards of normal. The shaded areas represent the limits within which lay 80 per cent of the data for free and total acid at the different ages. The heavy lines represent modes.

(chart 4). It is a remarkable fact that one can occasionally find free acid of 80 and more in apparently normal old men and women.

It is easy to say that the total range in our cases is from 0 to 108, but it is not so easy to say where one should place the limits of normal. It does not seem probable that with all our care in selecting the records for study, all of them came from normal persons. In chart 5 we have plotted for men and women modal free acidity at the different ages and on each side of these curves we have drawn other lines representing the

limits within which lie 80 per cent of our data. We might just as well have drawn other lines delimiting other fractions of the material, but so far as we know, there is no scientific reason for placing limits of normal at one point rather than at another.

TOTAL ACIDITY

The variations in total acidity can be studied in table 3 and chart 2. There it can be seen again that the distribution polygons tend to be bimodal owing to the existence of two different types of human beings: one with more or less free acid in the gastric juice, and the other without. Data from the latter group are responsible for the secondary mode to the left of the main one; again it was thought advisable to separate the two groups of data just as we did while studying free acidity. In plotting two polygons in place of one we used as ordinates percentages of the total group of data obtained from persons with and without acid, or in other words, the sum of the ordinates of the two polygons in each pair is 100. We were unable to make a satisfactory study of total acidity in children because the published reports of gastric analyses are rarely so complete that one can split them into two groups of those from persons with and those from persons without free acid.

COMBINED ACIDITY

An analysis of the combined acidity shows that there is no significant variation at any age, and no difference between the sexes. The values ranged between 6 and 40 units with a mean about 17. The range was so small that 90 per cent of the data fell between limits of 12 and 22 units. The combined acid in persons with achlorhydria appears to be only slightly (1 unit) less than in persons with free acid.

COMMENT

We began this study with the vague idea that after middle age gastric acidity might gradually decrease, and that this decrease might be due to progressive atrophy of the mucosa similar to that which takes place in the skin. Actually, now, since we know that there is no falling off in gastric acidity in older women, it does not seem probable that the decrease observed in the men can be due to senile changes because if there were such, one would expect them to be equally marked in the women.

Similarly, we can hardly ascribe the steady increase in the incidence of achlorhydria to atrophic changes that come with age because in that case we would expect the whole distribution curve of gastric acidity to move toward the left, that is, toward lower values, and we would expect

TABLE 3.—*Total Acid*

Group	Units of Acid	Males: Age, Years											Females: Age, Years									
		20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-79	Total	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-79	Total
With no free acid	1- 9	..	1	1	1	4	3	3	1	5	3	22	..	2	1	5	7	3	6	5	9	3	41
	10- 19	..	7	3	9	17	20	24	24	24	28	156	1	4	14	15	11	16	19	24	27	16	147
	20- 29	..	3	2	2	10	6	11	7	11	5	57	3	4	3	7	5	10	9	10	8	3	62
	30- 39	..	..	..	..	..	..	1	..	2	1	4	..	..	..	..	..	1	..	..	..	2	3
	40- 49	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	1
	Total	..	11	6	12	31	29	39	32	42	37	239	4	11	18	27	23	30	34	39	44	24	254
With free acid	10- 19	..	..	..	..	..	1	4	..	..	..	5	..	..	2	..	3	1	2	2	1	..	11
	20- 29	8	5	2	4	9	6	8	7	8	1	53	4	7	9	16	8	3	6	9	10	3	75
	30- 39	7	7	9	11	13	23	8	12	9	6	105	14	18	17	27	20	10	18	10	10	13	157
	40- 49	11	29	23	30	32	26	24	22	25	16	238	22	40	40	46	24	28	38	19	16	15	297
	50- 59	16	31	30	42	50	19	33	28	19	18	286	25	28	35	47	40	24	35	35	23	7	299
	60- 69	30	46	40	52	52	40	29	27	18	22	356	13	38	25	34	23	15	23	15	21	8	215
	70- 79	29	40	31	45	43	32	21	14	22	31	308	8	10	15	13	10	9	11	16	6	6	104
	80- 89	9	29	17	27	22	16	23	7	7	10	167	4	4	2	5	5	2	4	2	6	1	35
	90- 99	5	18	10	6	9	8	6	3	2	4	71	..	..	..	2	..	..	..	2	1	..	5
	100-109	1	3	..	3	2	3	2	..	3	3	20	..	..	..	..	..	..	..	..	1	1	2
	110-119	..	1	1	..	..	..	3	..	1	..	6	..	..	..	..	..	..	..	..	..	..	..
	Total	111	209	163	220	232	174	161	120	114	111	1,615	90	145	154	190	133	92	137	110	95	54	1,200
Median		65.8	67.1	64.4	64.4	62.3	63.0	61.2	56.8	57.9	56.5		52.0	52.7	50.0	51.2	52.5	51.7	51.3	54.3	54.5	47.4	
Mode		65.0	67.6	64.5	65.2	62.7	62.1	64.2	56.9	55.7	59.0		50.7	51.8	47.4	50.4	53.8	49.9	50.2	55.3	55.6	40.9	
Mean		64.6	66.9	64.3	64.0	62.1	61.0	62.0	56.8	58.9	55.3		52.7	53.1	51.3	51.6	51.8	52.6	51.9	53.8	53.9	50.9	
Probable error of mean		1.0	0.8	0.8	0.7	0.7	1.0	1.1	1.0	1.2	1.1		1.0	0.8	0.8	0.7	0.9	1.0	0.8	1.1	1.2	1.5	
Standard deviation		16.4	16.5	16.1	16.2	16.9	18.7	20.7	16.4	19.3	16.6		14.5	13.9	14.3	15.2	15.5	13.8	14.4	16.5	17.8	16.7	
Probable error of standard deviation		0.7	0.5	0.6	0.5	0.5	0.7	0.8	0.7	0.9	0.8		0.7	0.6	0.5	0.5	0.6	0.7	0.7	0.8	0.9	1.1	
Coefficient of variability		25.4	24.6	25.0	25.3	27.2	30.6	33.3	28.9	32.7	30.0		27.5	26.1	27.8	29.4	29.9	26.2	27.7	30.6	34.9	32.8	

to find some parallelism between this shift in both men and women and the increase in the incidence of achlorhydria. Actually there is no such parallelism in women and practically none in men.

Our impression, therefore, is that the process that gives rise to achlorhydria is different from the one which, in men, gradually reduces the degree of gastric acidity. There is much available evidence to indicate that the first process is inherited and that it partakes, perhaps, of the nature of mutation. Like many other defects, it can become uncovered at any time from birth to old age.

With the help of the data presented here, we hope to be able in future studies to detect with certainty small abnormalities in the secretory power of the stomach due to disease.

The trained statistician reviewing a study such as the one we are reporting will always want to know the range of a group of measurements made on one person. In other words, he will want to know the error of the method and the variation in the readings made on one individual day after day. Unfortunately, we cannot as yet give definite information on this point. The few studies reported thus far in the literature are vague, and the conclusions are not in agreement. Our own study designed to answer this question is now under way.

It is perhaps suggestive that duodenal ulcers so often appear in men between the ages of 20 and 25 years, about the time when the strength of the gastric acids is rapidly increasing. It would be more suggestive were it not for the fact that gastric ulcers usually do not make their appearance until the next decade. It may be that the three times greater incidence of ulcer in men than in women is associated with this decided difference in acidity.

There are so few things new under the sun that we do not dare to state that this big difference between the acidity in men and women has not been observed before; what we can say is that the fact was new to us.

SUMMARY

Satisfactory standards of normal gastric acidity have so far been lacking. A study has been made of data from 3,746 persons in whom careful examination did not reveal any disease which could conceivably affect the mucous membrane or the secretory activity of the stomach.

There was a steady increase in the incidence of achlorhydria from youth to old age. At the age of 60 years 28 women in 100 (in our series) failed to show free acid on repeated fractional analysis, and similarly, 23 men in 100 were achlorhydric. In an additional 5 per cent of women and 3 per cent of men there was no free acid in the first sample of an Ewald meal removed at the end of an hour.

Free gastric acidity appears to increase rapidly from childhood up to the age of 20 years when adult values are reached. About the age of puberty, the average value for boys begins to rise considerably above that for girls.

In order to simplify the statistical study of the group of persons with free acid all data from persons with true or apparent achlorhydria were first removed from consideration.

We can now say that modal free acidity for men ranges between 45 and 50 units in the years from 20 to 40. After this it falls off rapidly to a level of from 30 to 35 units in the aged. The mode for women is approximately 35 units throughout adult life. It appears to fall off slightly after the age of 60 years. The normal range of free acidity in both men and women is about 90 units.

Chart 4 shows that the modal total acidity for women is practically constant at a level of about 51 units between the ages of 20 and 60 years; the mode for men ranges from 66 at the age of 20 years down to 56 after the age of 65 years. For both free and total acidity, mean and modal values were about the same.

In both sexes the combined acidity appears to vary but little from youth to old age. Ninety per cent of the data lay between limits of 12 and 22 units with a mode at 17 units.

The data suggest that the process which gives rise to achlorhydria is not the same as the one that in men after 40 years produces a gradual falling off in acidity. The absence of such a gradual decrease in the older women makes it seem improbable that in either sex there is a progressive senile atrophy of the gastric mucosa.

THE SYSTEMIC EFFECTS OF HISTAMINE IN MAN

WITH SPECIAL REFERENCE TO THE RESPONSES OF THE CARDIOVASCULAR SYSTEM *

SOMA WEISS, M.D.

GEORGE P. ROBB, M.D.

AND

LAURENCE B. ELLIS, M.D.

BOSTON

The concept that histamine plays a fundamental rôle in the chemical control of the circulation is suggested by a series of observations by Dale and Lewis and their associates.[1] It is, however, remarkable that the evidence concerning histamine as a vasodilator substance in the physiologic regulation of the circulation is still largely based on indirect evidence and analogical observations. Direct proof for this function of histamine in the animal body is so far not available, and while the value of parallel and "teleologic evidence" in establishing a physiologic concept is considerable, it is recognized that concepts based on indirect evidence may be open to fallacy and therefore cannot be considered as proved.

Burn and Dale and their associates [2] observed a fall in the arterial blood pressure in anesthetized carnivorous animals. Lewis and his associates [3] presented evidence that the human skin, when subjected to various sorts of stimuli, reacts in the same manner as it does after intracutaneous puncture with small amounts of histamine. They claimed that the vasodilatation of the minute vessels of the skin follow-

* Submitted for publication, May 5, 1931.

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital, and the Department of Medicine of Harvard Medical School.

1. Barger, G., and Dale, H. H.: The Presence in Ergot and Physiological Activity of B-Imidazolylethylamine, J. Physiol. **40**:38, 1910. Dale, H. H., and Laidlaw, P. P.: The Physiological Action of B-Imidazolylethylamine, J. Physiol. **41**:318, 1910. Dale, H. H., and Richards, A. N.: The Vasodilator Action of Histamine and of Some Other Substances, J. Physiol. **52**:110, 1918. Dale, H. H., and Laidlaw, P. P.: Histamine Shock, J. Physiol. **52**:355, 1919. Lewis, T.: The Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

2. Burn, J. H., and Dale, H. H.: The Vasodilator Action of Histamine, and Its Physiological Significance, J. Physiol. **61**:185, 1926.

3. Lewis (footnote 1).

ing these stimuli is due to a substance or substances closely related to histamine. The implication of these observations is that Lewis' H-substance, or histamine, preexists in the cutaneous cells, and is liberated to exert its physiologic rôle only in response to certain stimuli. Best, Dale, Dudley and Thorpe [4] and Thorpe [5] demonstrated that when tissues are extracted by a relatively simple chemical procedure, appreciable or large amounts of histamine are obtained. The extract of the lung was found to contain from about ten to twenty times more histamine than the majority of the organs tested, 1 Kg. of fresh lung tissue yielding as much as 75 mg. of histamine. It is also significant that, according to Dale,[6] the vasodilator effect of various organ extracts used therapeutically depends entirely on their combined histamine and choline content. Dale and Laidlaw [7] observed that anesthetized cats, following the sudden and continuous injection of histamine, exhibit a condition resembling in many respects traumatic and surgical shock in man. Cannon [8] produced evidence that some chemical substance, probably histamine or a substance related thereto, is actually responsible for the manifestations of traumatic shock.

All these observations strongly suggest, then, the active rôle of histamine in the regulation of the normal and abnormal circulation. There are, however, numerous studies reported in the literature that contradict this concept of the physiologic rôle of histamine. Contrary to the behavior of epinephrine, histamine produces varying effects on the vascular system and the minute vessels of different species of animals. Furthermore, the same species of animals may behave differently under diverse conditions.

Histamine produces a fall in the blood pressure of carnivorous animals, and an elevation in rodents. Feldberg's observations in Dale's laboratory [9] suggest that these variations in the effect of histamine on the blood vessels of different species of animals are more apparent than real, as the effect depends on the tone of the vessels rather than on the species. The evidence presented by Feldberg in support of this

4. Best, C. H.; Dale, H. H.; Dudley, H. W., and Thorpe, W. V.: The Nature of the Vaso-Dilator Constituents of Certain Tissue Extracts, J. Physiol. **62**:397, 1927.

5. Thorpe, W. V.: Vasodilator Constituents of Tissue Extracts: Isolation of Histamine from Muscle, Biochem. J. **22**:94, 1928.

6. Dale, H. H.: Some Chemical Factors in the Control of the Circulation, Lancet **1**:1233, 1929.

7. Dale and Laidlaw (footnote 1, fourth reference).

8. Cannon, W. B.: Discussion sur le choc traumatique, Mém. Soc. de biol. **81**: 854, 1918; The Course of Events in Secondary Wound Shock, J. A. M. A. **73**:174 (July 19) 1919; Traumatic Shocks, Surgical Monographs, New York, D. Appleton & Company, 1923.

9. Feldberg, W.: The Action of Histamine on the Blood Vessels of the Rabbit, J. Physiol. **63**:211, 1927.

conception is not conclusive, however, and thus the "histamine paradox" must be considered unsettled. Burn and Dale [2] explained the difference in the behavior of animals by the variation of the level at which the constrictor effect of histamine on the central portion of the vascular tree changes to a dilator effect on the peripheral portion. In the dog, for example, the constrictor effect of histamine on the arterial tree changes to a dilator effect at the level of the small visible arteries. In the cat, there is a constrictor effect to the level of the arterioles and capillaries, which, under certain conditions, dilate in response to histamine. In rodents the appearance of the constrictor effect is pushed to the periphery.

It is rather significant that Grant and Jones [10] found that the minute vessels of the skin and mucous membranes of the tongue of the frog respond similarly to those of man with dilatation of the small blood vessels under local stimulus, and yet that histamine produces no dilatation of the blood vessels when applied either locally or systemically, although histamine has been extracted from the skin of the frog. It is rather difficult to reconcile these variations in vascular response produced by a substance that is supposed to play a uniform regulatory rôle in the circulation. There is, furthermore, a significant discrepancy between the short duration of action of histamine on entering the blood stream and the relatively long duration of certain vasodilator responses attributed to histamine. Here, again, assumptions have been made that histamine or allied substances may be combined with colloids or other substances that alter its persistence of action. Experimental proof for such a statement again is not available.

A considerable gap also exists between the finding of as much as 75 mg. per kilogram of histamine in fresh lung tissue and the opinion of Dale [6] that histamine has "evidently as good a claim to be regarded as a normal constituent of the living cell, as has any other substance which similarly conservative methods could extract." If such small amounts of histamine as 0.1 mg. produce profound changes in the minute blood vessels in man, it is difficult to realize how an amount that is many times that of the fatal dose can be attached to the endothelial system of the lungs without exerting any influence on the pulmonary capillaries. Not only is the significance of these apparently contradictory observations obscure, but the interpretation of the observations on the same species is not agreed on (Mautner and Pick [11]).

10. Grant, R. T., and Jones, T. D.: The Effect of Histamine and of Local Injury on the Blood Vessels of the Frog: A Vasodilator Substance in Extracts of Frog's Skin, Heart **14**:337, 1929.

11. Mautner, H., and Pick, E. P.: Ueber die durch "Shockgifte" erzeugten Zirkulationsstörungen, München. med. Wchnschr. **62**:1141, 1915; II. Das Verhalten der überlebenden Leber, Biochem. Ztschr. **127**:72, 1922.

The considerations outlined strongly suggest how hazardous it is to define the rôle of histamine in health or in disease from animal observations. The necessity of obtaining direct information from studies on man is obviously great. The study presented here deals mainly with the systemic effect of histamine in human beings. It is fully appreciated that the results of these observations do not necessarily apply to the alleged regulatory functions of histamine between cell and local capillary blood supply where the physiologic relationship is different. The inquiry was centered rather on the influence of histamine on the circulation, metabolism and respiration, as these three functions are closely interrelated, and adjustments in one often produce changes in the others. The response of other bodily functions to histamine was also studied. Whenever possible, quantitative observations were made. The procedures followed in the observations will be described under the proper headings. Although, for clarity, the results obtained are presented in groups, actually, numerous bodily functions were studied simultaneously in the same subject. Simultaneous observations are a safeguard against faulty conclusions and aid considerably in interpreting correctly the interrelations between bodily functions.

In our experience, histamine has been found to have no effect on the cardiovascular system when given orally to man. Several hundred times the fatal intravenous dose, given by mouth, failed to produce appreciable signs or symptoms. On the other hand, histamine is absorbed promptly from the subcutaneous depot, although individual variation in its speed of absorption complicates studies in which comparative quantitative observations are desired. Furthermore, the amount of histamine entering the blood stream from the subcutaneous tissues varies considerably at different time intervals. In order to avoid these variations, the intravenous channel of administration was adopted in a majority of the observations. The effects of both a single intravenous injection and of continuous intravenous infusion were studied. The intravenous method of administration makes the results obtained on different subjects comparable, and since the amount of histamine entering the blood stream in a given unit of time is known, and the persistence of action of histamine, as will be shown, is presumably of short duration, a quantitative relationship can be established between the concentration of histamine in the blood stream and the degree of changes in bodily functions.

Throughout the course of this study, histamine phosphate was used. All figures of "histamine" express amounts of histamine phosphate unless specifically characterized as "histamine base." [12]

12. The molecular weight of histamine phosphate is approximately thrice that of histamine base.

THE EFFECTS OF THE RAPID INTRAVENOUS ADMINISTRATION OF SINGLE DOSES OF HISTAMINE

As described in a previous communication [13] and also reported by others,[14] the sudden single intravenous injection of histamine is followed by a sensation of warmth over the face associated with intense flushing. Depending on the dose administered, the flush may spread to various skin areas toward the feet. There may also be a throbbing sensation over the head with or without headache. Following toxic doses, nausea and vomiting may develop. The heart rate shows an elevation.

Observations on more than a hundred subjects with a normal cardiovascular system established the minimal single dose, just sufficient to produce detectable changes in the minute vessels of the face or an elevation in the cardiac rate, as varying between from 0.01 to 0.03 mg., corresponding to from 0.00015 to 0.0005 mg. per kilogram of body weight. A tenfold increase of these minimal amounts occasionally may produce toxic manifestations. In the majority of instances amounts of 0.07 mg. or 0.001 mg. per kilogram of body weight were administered in a solution of 1 : 10,000 concentration.

Changes in the Normal Complexes of the Electrocardiogram.—In order to ascertain the possible direct effect of histamine on the coronary circulation or the cardiac musculature, continuous electrocardiographic tracings of lead II were taken following the injection of from 0.05 to 0.08 mg. of histamine into fifteen subjects with a normal cardiovascular system. The onset of the peripheral vascular responses due to histamine was registered by the electrocardiographic tracings through instantaneous temporary short-circuiting of the galvanometer. Analysis of the records thus obtained indicated that the onset of the acceleration occurs simultaneously or from two to three seconds before the onset of the peripheral vascular responses. Simultaneously with this acceleration, the T wave shows a progressive depression. With the return of the normal cardiac rate, the T wave assumes its original shape. Figure 1 represents a typical observation. These changes in the T wave, interpreted in the light of present knowledge, indicate that histamine induces a change in the coronary blood vessels or the musculature. The more exact mechanism or nature of this effect is not clear at present.

13. Weiss, S.; Robb, G. P., and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels, Am. Heart J. **4**:664, 1929.

14. Eppinger, H.: Ueber eine eigentümliche Hautreaktion hervorgerufen durch Ergamin, Wien. med. Wchnschr. **63**:1414, 1913. Harmer, I., and Harris, K. E.: Observations on the Vascular Reactions in Man in Response to Histamine, Heart **13**:381, 1926.

Heart Rate and Arterial Blood Pressure.—Following the administration of an average dose of 0.001 mg. of histamine per kilogram, an elevation in the cardiac rate regularly appears after an interval of from fifteen to twenty-five seconds, corresponding to the circulation time. The maximal average elevation is 15 heart beats per minute, and this usually occurs within one minute after the injection. In a number of instances the maximal rise in the heart rate was from 30 to 40 beats.

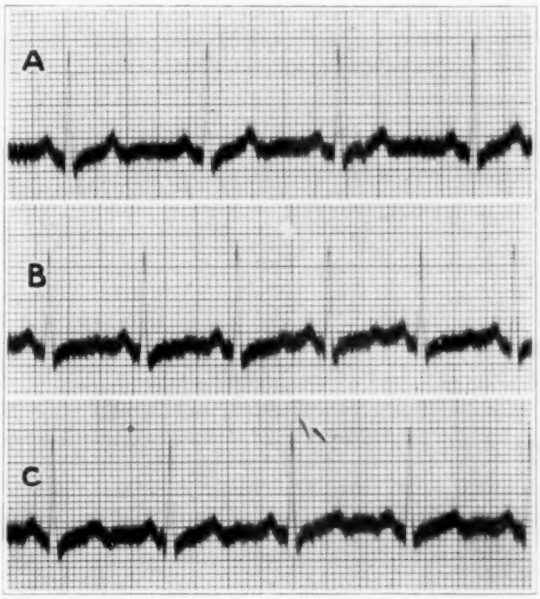

Fig. 1.—The effect of the sudden intravenous injection of 0.05 mg. of histamine phosphate on the normal complexes of the electrocardiogram. *A* indicates a control tracing; *B*, a tracing thirty seconds after the injection; note the increase in rate and the depressed T wave; *C*, a tracing fifty seconds after the injection; the T wave is approaching its normal shape. All tracings are of lead II.

With this elevation of the heart rate, moderate changes in the arterial blood pressure occasionally developed. No change, or a rise of as much as 15 mm. of mercury in the systolic and diastolic blood pressures, occurred in the majority of instances (forty-two subjects). A fall of similar order was observed in a small group (eight subjects). The duration of the flush and changes in the cardiac rate and arterial blood pressure lasted from two to five minutes.

Venous Pressure.—The venous pressure, as measured continuously by the method of Moritz and Tabora,[15] showed no appreciable changes. Occasionally there was a rise corresponding to 1 or 3 cm. of water in the venous pressure. Table 1 presents a few of the observations on the effect of a single dose of histamine on the arterial and the venous pressures.

The Response of the Cerebral and Facial Blood Vessels.—Lewis[14] has shown that the minute vessels of the face are especially sensitive to histamine. Our observations indicate that the minute vessels of the brain of man also react to small amounts of histamine. Following the administration of an average single dose of histamine, after an elapse of a period corresponding to the circulation time between the site of the injection and the brain,[13] there is a prompt rise in the intra-

TABLE 1.—*The Effect of a Single Intravenous Injection of Histamine on the Arterial and Venous Blood Pressure*

Observation	Histamine Injected Into Vein, Mg.	Histamine per Kg. Injected Into Vein, Mg.	Circulation Time, Sec.	Vital Capacity per Sq. Meter of Body Surface, Cc.	Arterial Blood Pressure				Venous Blood Pressure	
					Systolic		Diastolic			
					Before, Mm. Hg	After, Mm. Hg	Before, Mm. Hg	After, Mm. Hg	Before, Cc. H_2O	After, Cc. H_2O
1	0.06	0.001	22	2,400	140-148	140-142	86-92	80-92	6-7	6-7
2	0.07	0.001	32	2,100	164-172	168-174	44-46	48-58	1-2	1-3
3	0.06	0.001	22	2,450	110-112	108-114	70	65-72	4-5	4-7
4	0.08	0.001	20	2,700	135-138	130-137	85	80-85	3	3-4
5	0.08	0.001	25	2,400	125-120	115-125	60-70	58-70	3-4	3-5
6	0.07	0.001	18	2,100	110-120	110-125	65-80	60-80	1-2	1-2
7	0.08	0.001	20	2,500	126-132	118-135	70-75	70-80	6-7	5-7

cranial pressure, as indicated by the changes in the fluid level of the manometer connected with the subarachnoidal space. Simultaneously with the onset of this rise in the pressure of the cerebrospinal fluid, the cardiac pulsatile expansion of the spinal fluid increases to three or four times normal. This usually lasts several minutes after the return of the cerebrospinal fluid to its initial level (table 2). In observations in which the arterial and venous pressures were measured simultaneously with the cerebrospinal pressure, it was found that the rise in the spinal pressure, as well as the increase in the pulsatile expansion of the spinal fluid, may occur without necessary alteration either in the arterial or in the venous pressure.

Such a rise in the spinal pressure with increased pulsatile expansion and without simultaneous change in the arterial and venous pressure can be attributed only to a dilatation of the arterioles, capillaries and venules, which results in an increase in the volume of blood in the brain.

15. Moritz, F., and Tabora, D. V.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exact zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.

That this inference is indeed correct has been substantiated by direct observation of the effect of histamine on minute vessels of the brain. In cases in which the brain surface was exposed for removal of a neoplasm, the intravenous administration of from 0.05 to 0.1 mg. of histamine was followed by a prompt expansion of the brain volume associated with a marked increase in the cerebral pulsation and the appearance of a bright flush. These changes lasted for from ninety to one hundred and twenty seconds.

The following case gives a summary of one of these observations:

A. McE., aged 21, was operated on for the removal of an intracranial neoplasm. Ether anesthesia was used. A large round area of the skull over the right temporoparietal area was removed, and the dura was opened. The exposed brain area was clear. The heart rate was 76 per minute; the arterial systolic blood pressure was

TABLE 2.—*The Effect of Histamine on the Intracranial Pressure*

Observation	Histamine Injected Into Vein, Mg.	Histamine per Kg., Mg.	Arm—Face Circulation Time, Sec.	Arm—Brain Circulation Time, Sec.	Intracranial Pressure Maximum			
					Before, Mm. H_2O	After, Mm. H_2O	Maximum Elevation, Mm. H_2O	Duration of Rise, Sec.
1	0.07	0.001	13	12	140	250	110	90
2	0.05	0.001	14-15	15	140	290	150	105
3	0.07	0.001	17	16	110	280	170	90
4	0.06	0.001	16	17	100	300	200	75
5	0.02	0.0005	19	17	175	290	115	80
6	0.08	0.001	19	19	230	350	120	100
7	0.10	0.002	19	20	185	250	65	80
8	0.08	0.001	21	22	75	200	125	..

100 mm. of mercury; the diastolic pressure, 50 mm. Nine-hundredths milligram of histamine phosphate in a solution of 1:5,000 was injected into the foot vein. Fourteen seconds later a distinct increase of the pulsation of the brain was noted, and simultaneously there were an appreciable swelling and bulging. The surface of the brain became pink, and even the small visible vessels (presumably veins) became engorged. The cardiac rate rose to a maximum of 82 beats per minute. These changes reached their maximum in from thirty to thirty-five seconds after the onset and disappeared in three minutes. There was no appreciable change in the arterial blood pressure. Five minutes later 0.1 mg. of histamine was again injected into the foot vein with an identical effect.

That the arterioles and other minute vessels of the human brain respond with dilatation to histamine was further substantiated by a third set of observations in which the oxygen difference between the arterial blood and the venous blood obtained from the internal jugular vein was studied before and after the administration of histamine.[16]

16. Weiss, S.; Lennox, W. G., and Robb, G. P.: The Dilator Effect of Histamine on the Cerebral Vessels in Man, Proc. Soc. Exper. Biol. & Med. **26**:706, 1929. Weiss, S., and Lennox, W. G.: The Cerebral Circulation: XVII. Cerebral Blood Flow and the Vasomotor Response of the Minute Vessels of the Human Brain to Histamine, Arch. Neurol. & Psychiat. **26**:737 (Oct.) 1931.

The vessels of the eyeground failed to reveal obvious changes following the administration of histamine.

The observations presented establish the fact that the arterioles and the minute vessels of the brain respond with dilatation following the intravenous administration of histamine. In order to establish a quantitative index as to the relative sensitivity of the cerebral blood vessels, the minimal effective dose that produced dilatation in the cerebral vessels as indicated by the rise in cerebrospinal pressure and an increase in pulsatile movements was compared with the minimal dose that produced a flush in four subjects in whom puncture of the subarachnoid space was performed for therapeutic purposes. Table 3 presents the results of a few of these observations. In the instances presented, although the minimal dose (table 3) failed to produce changes

TABLE 3.—*The Relative Sensitivity of the Cerebral Blood Vessels to Histamine, as Compared with That of the Facial Vessels*

Observation	Histamine Injected Into Vein, Mg.	Histamine per Kg., Mg.	Onset of Flush, Sec.	Onset of Rise in Intracranial Pressure, Sec.	Maximum Intracranial Pressure After Histamine, Mm. H_2O		Maximum Rise by Histamine, Mm. H_2O	Duration of Rise in Intracranial Pressure, Sec.
					Before	After		
1	0.02	0.0003	..	16	120	180	60	120
	0.04	0.0006	17	16	110	250	140	115
	0.07	0.0010	17	17	125	300	175	130
2	0.005	0.0001	..	17	170	220	50	80
	0.025	0.0006	19	17	175	290	115	80
3	0.02	0.0002	..	24	150	350	200	100
	0.03	0.0003	26	24	190	480	380	110
4	0.01	0.0002	..	26	65	110	55	130
	0.03	0.0006	26	26	40	100	60	120

in the facial vessels, there was a response in the cerebral vessels as indicated by both the elevated intracranial pressure and the increase in the pulsatile expansions. It would appear, then, that the sensitivity of minute blood vessels of the human brain to histamine is unusually great; probably greater even than that of the minute vessels of the face, which has been considered the vascular area most sensitive to histamine.

Cutaneous Blood Flow of the Face.—As the flush is most intense over the face, the change of the blood flow in this area following the appearance of the flush was measured by determining the skin temperature with the aid of a thermocouple connected with a calibrated galvanometer.[17] In one group of subjects, with the development of a bright red flush, there was a rise in the skin temperature of as much as 2.5 C. (36.5 F.), indicating an increase in the blood flow. In another group such changes were not deserved. The latter group tended to develop a cyanotic flush.

17. Benedict, F. G.: Die Temperatur der menschlichen Haut, Ergebn. d. Physiol. **24**:594, 1925.

Blood Flow Through the Capillaries of the Finger-Nail Bed.—With the aid of a special microscope, repeated observations were made on the shape of the capillaries of the finger-nail bed and on the blood flow through them after the injection of from 0.02 to 0.1 mg. of histamine. Such amounts of histamine induced no flush over the fingers. No changes in the shape of the capillaries was noted. Coinciding with the onset of the flush over the face, there was an increase in the velocity of the blood flow.

THE EFFECTS OF THE CONTINUOUS INTRAVENOUS ADMINISTRATION OF HISTAMINE IN MAN

In studying the effect of the continuous intravenous administration of histamine, solutions of various concentrations, from 1 : 100,000 to 1 : 5,000, were employed. Histamine phosphate was dissolved in sterile physiologic solution of sodium chloride, the concentration of which, as determined by its freezing point, was 0.89 per cent. A special arrangement permitted continuous uniform infusion of the desired amount of histamine. It was also possible to change from one concentration of solution to another or to a physiologic solution of sodium chloride. An infusion of saline, as a control solution, preceded each administration of histamine.

The subjective sensations following the continuous infusion of histamine are essentially those experienced after the injection of a subcutaneous or a single intravenous dose. A sensation of heat over the face, fulness over the head and slight palpitation follow infusion of minimal effective amounts. Increase in the rate of injection is associated with fulness of the head, a pulsating headache, palpitation, perspiration nausea and vomiting. Headaches occur less often and with less severity providing the rate of injection is increased gradually, when relatively large continuous doses are given than after the injection of a single dose. It appears that sudden change in concentration plays an important rôle in precipitating headaches. It seems especially significant that, regardless of the duration of the infusion, the intensity of the symptoms remains essentially unchanged as long as the rate of injection is unaltered. Often, the symptoms become less severe with the progress of time.

The Susceptibility of Man to Histamine.—The minimal effective dose manifests itself in a slight elevation of the cardiac rate and in dilatation of the minute vessels of the face. If a subminimal dose is infused, such responses are not observed even when the same rate is maintained for hours. If histamine is infused at a rate greater than that of the minimal dose, a response of the cardiovascular system follows, the intensity of which depends entirely on the rate

but not on the duration of the injection. These observations clearly demonstrate that histamine is changed to a pharmacologically ineffective substance or substances practically as fast as it is infused into the human circulation. For this reason, by determining the rate of injection of a subminimal and a minimal effective rate, one can estimate the susceptibility of the cardiovascular system of man to histamine. Furthermore, because the response of the minute cutaneous blood vessels and the cardiac rate occurs earlier than the other bodily reactions, the minimal dose represents the sensitivity of man to hista-

TABLE 4.—*The Minimal Dose of Histamine Effective in Man*

Observation	Age	Histamine, Mg. per Min.	Concentration of Histamine Injected	Histamine, Mg. per Kg. per Min.	Heart Rate per Min.	Arterial Blood Pressure		Response of Facial Vessels
						Systolic, Mm. Hg	Diastolic, Mm. Hg	
1	35	0.01	1:10,000	0.00018	78	125	80	—
2		0.02	1:10,000	0.00036	96	128	84	+
3	29	0.01	1:50,000	0.00018	80	118	70	—
4		0.02	1:50,000	0.00036	88	122	68	+
5	29	0.01	1:50,000	0.0001	76	132	78	+
6	25	0.006	1:100,000	0.00008	72	128	66	—
7		0.012	1:100,000	0.00015	72	128	60	+
8	24	0.004	1:100,000	0.00006	82	126	76	—
9		0.006	1:100,000	0.00008	82	124	70	+
10	25	0.004	1:100,000	0.00006	60	104	68	—
11		0.01	1:100,000	0.00016	64	104	70	+
12	24	0.005	1:100,000	0.00006	72	110	90	—
13		0.010	1:100,000	0.00012	72	114	94	+
14	32	0.004	1:10,000	0.00007	80	90	60	—
15		0.007	1:10,000	0.00012	80	90	60	+
16	17	0.005	1:10,000	0.00012	66	98	68	—
17		0.007	1:10,000	0.00016	68	98	70	+
18	40	0.006	1:10,000	0.00006	80	138	80	—
19		0.012	1:10,000	0.00012	80	138	78	+
20	62	0.004	1:10,000	0.00008	68	130	68	—
21		0.008	1:10,000	0.00016	70	132	68	+

mine. Such observations permit also the estimation of the minimal effective dose of histamine in the blood stream. Table 4 presents these observations. The minimal effective dose varied from 0.006 to 0.02 mg. per minute, with an average rate of 0.01 mg. Although the age of the subjects varied from 17 to 65, the variation in age did not influence the susceptibility of the subjects.

Changes in the Normal Complexes of the Electrocardiograms.—The influence of the continuous intravenous administration of histamine on the complexes of the normal electrocardiogram has been studied in the manner described. Progressively larger doses were administered. Analysis of the tracings indicate that histamine in doses as small as 0.004 mg. per minute may depress all the complexes of the electrocardiograms. The effect is especially marked on the T wave. The degree of the depression or inversion is to a certain extent propor-

tional to the rate of administration. Figures 2 and 3 represent two of the observations made. Subject G.M. (fig. 2), aged 27, received, following a control tracing, progressively increasing amounts of histamine from 0.006 mg. per minute to 0.04 mg. per minute. The T wave exhibits a progressive depression, although even such large amounts as 0.04 mg. per minute, corresponding to 2.4 mg. per hour, failed to invert the T wave. In the case of subject L.M.D. (fig. 3), aged 16, on the other hand, 0.012 mg. per minute produced an inversion of the T wave. These changes in the T wave disappeared within a few

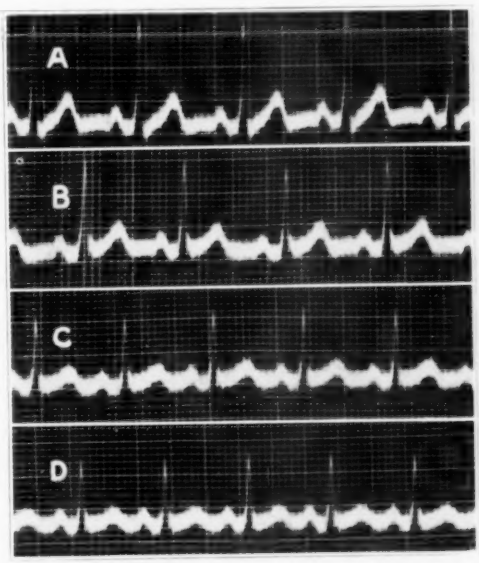

Fig. 2.—The effect of the continuous intravenous administration of histamine on the complexes of the normal electrocardiogram. *A* indicates a control tracing; *B*, a tracing with an injection rate of 0.01 mg. per minute; *C*, a tracing with an injection rate of 0.02 mg. per minute; *D*, a tracing with an injection rate of 0.04 mg. per minute. Tracings *B*, *C* and *D* show a progressive decrease in the T wave. All tracings are of lead II.

minutes after the infusion of histamine stopped. The results and the interpretations of these observations are identical to those described after the sudden injection of histamine.

Heart Rate and Arterial Blood Pressure.—Figure 4 presents the relationship between the dosage of histamine and the cardiac rate. The duration of the infusion at an even rate lasted from fifteen to twenty

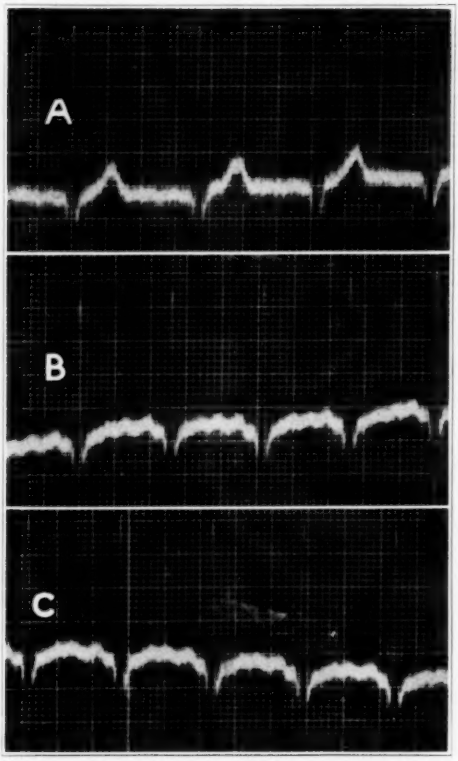

Fig. 3.—The effect of the continuous intravenous administration of histamine on the complexes of the normal electrocardiogram. *A* indicates a control tracing; *B*, a tracing with an injection rate of 0.012 mg. per minute; *C*, a tracing with an injection rate of 0.016 mg. per minute. In tracings *B* and *C* the T wave is inverted. All tracings are of lead II.

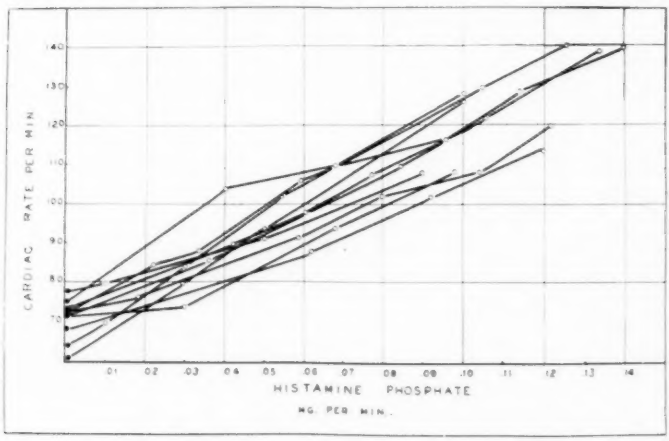

Fig. 4.—The relationship between the infusion of histamine and the cardiac rate. The dark dots represent the average of the control heart rates before the administration of histamine; the small circles, the average cardiac rate in response to various rates of infusion of histamine, each of which lasted from fifteen to twenty minutes.

minutes. The dots of the curves represent an average of several readings at the same rate of injection. Increasing amounts of histamine were administered to the same subject. The degree of elevation of the cardiac rate was unchanged when the same rate of injection was maintained, although if the rate was maintained for a longer period, such as an hour or two, the cardiac rate gradually became elevated. An increase in the amount injected per minute produced a progressive rise in the cardiac rate. In addition to the observation charted, in a number of instances higher amounts of histamine were infused, up to 0.4 mg. per minute. The elevation of the cardiac rate above 120 was relatively slight even when the dose was increased considerably. The maximal rate per minute was observed after the injection of 0.4 mg. per minute. The maintenance of this rate of injection for one hour was accompanied by toxic symptoms, which made further increase of rate undesirable. The general behavior of the subject and the cardiovascular system in these observations was not similar to the description of experimental histamine shock.

Intravenous injection of a single dose of histamine as a rule fails to produce a fall in the arterial blood pressure in normal subjects. Because histamine is rapidly destroyed in the human body, it seemed desirable to investigate the effect of continuous injections of histamine on the arterial blood pressure. Observations on certain species of animals seemed to justify the assumption that histamine would also lower the arterial blood pressure of man. This alleged effect certain investigators considered significant in shock and other abnormal states of the body.

The arterial blood pressure was measured by the Riva-Rocci mercury manometer, and in a number of instances was also graphically recorded with the Tycos apparatus. The arterial blood pressure was determined repeatedly on forty subjects with a normal cardiovascular system. In addition, a special study of the blood pressure was made on ten normal subjects to whom progressively increasing doses, as indicated in figures 5 and 6, were administered. The rate of dosage varied from 0.01 to 0.13 mg. per minute, and the duration of the injection lasted from fifteen minutes to two hours at each rate of injection. The curves of these ten subjects parallel the findings of the larger unrecorded groups. The systolic blood pressure was essentially unaltered. Some cases tended to show slight elevation, but the average curve of the systolic blood pressure was essentially a horizontal line. The diastolic blood pressure showed no uniform change, its average curve showing a slight tendency to fall as the rate of injection reached 0.08 mg. per minute or above. Considering that the injection at such a relatively high rate

as from 0.08 to 0.14 mg. per minute is associated with intense systemic reaction and with a marked elevation of the cardiac rate, it was surprising to observe the lack of any uniform lowering of the systolic and diastolic blood pressures.

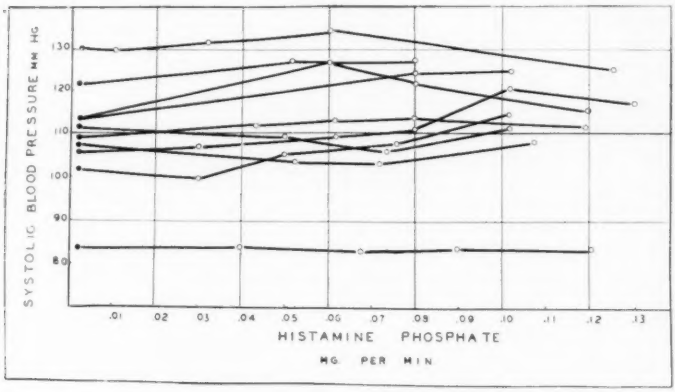

Fig. 5.—The effect of the continuous intravenous infusion of histamine on the systolic arterial blood pressure.

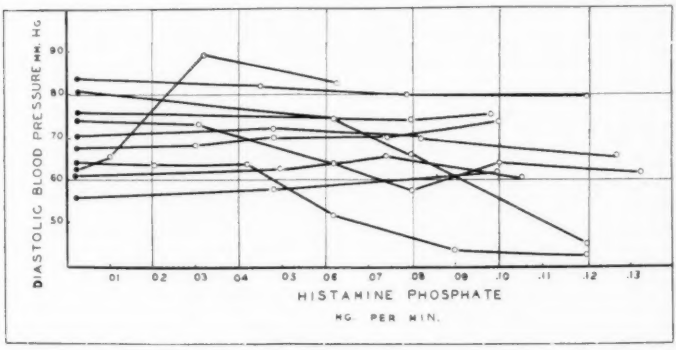

Fig. 6.—The effect of the continuous intravenous infusion of histamine on the diastolic arterial blood pressure.

Venous Pressure.—In ten subjects in whom the effect of gradually increased amounts of histamine on the arterial blood pressure and on the cardiac rate were studied, additional observations were made on the venous pressure as measured by the Moritz and Tabora method.[13] Either no change or a moderate rise, which in three instances was 3.5 cm. of water, was observed. The average venous pressure before

the administration of histamine was 6 cm.; during the administration of histamine, 7.4 cm.

Capillary Pressure.—In five subjects the pressure in the minute vessels of the skin was measured according to the method of Lewis and Haynal [18] at the height of the histamine effect. Both the open and the closed capsules were employed. The results of these measurements showed that the pressure in the minute vessels varied between 10 and 18 mm. of mercury, with an average of 16 mm., as contrasted with a variation of from 6 to 12 mm. of mercury, with an average of 9 mm., obtained on subjects without the histamine effect. These results indicate but a slight arteriolar dilatation during the height of the histamine effect following the administration of from 0.1 to 0.2 mg. per minute, as contrasted with the marked arteriolar dilatation that followed the direct cutaneous puncture of histamine 1:1,000. In a previous communication,[19] it was shown that following such a cutaneous puncture of histamine, the capillary pressure rises to from 40 to 60 mm. of mercury, with an average value of 55 mm.

The Response of the Cerebral Vessels.—In a group of five subjects on whom spinal puncture was performed for diagnostic purposes, the effect of the continuous intravenous infusion of histamine on the cerebral vessels, when administered in increasing amounts, was studied. Again, the observation was made that minimal amounts of histamine, at a rate of from 0.003 to 0.008 mg. per minute, which were insufficient to produce an increase of the heart rate or a dilatation of the cutaneous blood vessels, produced an increase in the pulsatile expansion of the cerebrospinal fluid. This expansion often was not associated with a rise in the spinal pressure. With an increase in the rate of the injection, the degree of pulsation increased, and there was also a rise in the spinal pressure. The height of the increase in the cerebrospinal pressure depended on the amount of histamine injected and on the degree of change from one dose to another. The rise following the injection of 0.1 mg. per minute was usually from 150 to 200 mg. of water. With the maintenance of the rate for longer than ten minutes, the pressure often returned to normal, but the increased oscillation continued unaltered as long as the injection of histamine continued.

Our interpretation of these observations is that with the administration of histamine there is a dilatation of the minute vessels, resulting

18. Lewis, T., and Haynal, I.: Observation Relating to the Tone of the Minute Vessels of the Human Skin: With Remarks upon and Illustrations of Measurements of Pressure Within These Vessels, Heart **14**:177, 1928.

19. Ellis, L. B., and Weiss, S.: The Measurement of Capillary Pressure Under Natural Conditions and After Arteriolar Dilatation, in Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, J. Clin. Investigation **8**:47, 1929.

in an increase in the volume of the brain and hence in an increase in the spinal pressure. The increased oscillatory movements, in the absence of changes in arterial and venous pressure, are due to dilatation of the arterioles and perhaps of other minute vessels. If the infusion of histamine is maintained, the elevation in spinal pressure caused by the increased volume of the brain disappears, perhaps because of an increased absorption of the spinal fluid; but the oscillatory movements are unchanged because the arterioles continue to be in a state of relaxation.

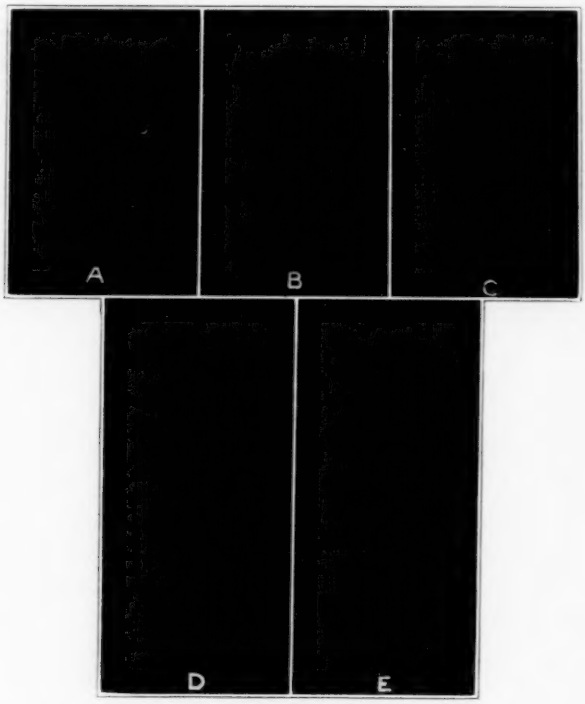

Fig. 7.—The dilator effect of histamine on the pulsatile expansions of the cerebral blood vessels. *A* indicates a control tracing; *B*, a tracing with an injection rate of 0.02 mg. per minute; *C*, a tracing with an injection rate of 0.05 mg. per minute; *D*, a tracing three minutes after the injection of histamine was stopped; *E*, a tracing ten minutes after the injection of histamine was stopped.

Another opportunity to demonstrate the effect of histamine on the cerebral blood vessels was given through observations on a patient with a cranial defect as the result of an operation for the removal of a neoplasm. The pulsation of the brain was registered with the aid of a flat, round oncometer applied over the cranial defect. Part of the

results of these observations are given in figure 7. As indicated, immediately after the administration of histamine at a rate of 0.02 mg. per minute, there was a marked increase in the pulsatile expansion of the brain. This increase continued as long as the histamine was being infused. With cessation of the histamine, the pulsation returned to normal within ten minutes. The arterial and venous blood pressures remained unaltered during the administration of histamine.

These vascular reactions following the continuous administration of histamine are of the same character as those that follow the injection of a single dose of histamine.

The Response of the Cutaneous Blood Vessels.—The flush that follows the administration of histamine is one of its most striking effects. The nature of this reaction was investigated in a long series of experiments. Increasing amounts of histamine were injected into normal subjects, and the change in color of the skin was compared with that of the skin temperature at various standard areas over the face, chest, arms, abdomen and lower extremities. The temperature of the skin was measured with a thermocouple. The room temperature was kept as constant as possible. Even under such experimental conditions, considerable spontaneous fluctuation of the skin temperature was observed in certain subjects. Following several control observations with and without intravenous injection of saline, the administration of histamine was started and the measurements of the skin temperature repeated frequently at from five to ten minute intervals.

The color of the skin depends largely on the state of the subpapillary venules and, to a lesser degree, of the capillary bed.[8] A flush, therefore, may be due to a dilatation of the venules alone or to a dilatation of the venules together with the arterioles and capillaries. If there is arteriolar dilatation, the blood flow through the flushed skin area increases, and the degree of increase in blood flow is indicated by an elevation of the skin temperature.

A study of the reaction of the cutaneous blood vessels to histamine in thirty normal subjects indicates that the vascular response is not uniform. As suggested in a previous communication,[20] the sensitivity of the minute vessels generally decreased progressively from head to foot. The flush, however, even within the same anatomic area, is not always uniform. In one group of subjects the flush did not proceed downward diffusely with increasing dosage, but the skin areas assumed a mottled appearance with blotchy white islands in the midst of the deep red, flushed areas. The blood vessels within the white areas were apparently relatively resistant to histamine. With elevation of

20. Weiss, S., and Ellis, L. B.: The Circulatory Mechanism and Unilateral Edema in Cerebral Hemiplegia, J. Clin. Investigation **9**:17, 1930.

the dosage, they often became red. On repeated experiments, the same subject as a rule responded with a mottled flush. In a number of instances, when the same rate of injection was maintained for over an hour, it was observed that the intensity of flush had a tendency to become less and that the mottled white areas gradually increased. These variations in the response of the cutaneous blood vessels may offer an explanation of the individual variations observed in the dermal manifestation of certain diseases.

All the subjects responded with flush, and the appearance of the flush over different skin areas and the dose required to produce it were fairly uniform. However, not all subjects responded with an elevation of the skin temperature. Of the twenty-five subjects, there were six who, even with such large amounts of histamine at 0.2 mg. per minute up to the appearance of the toxic manifestation, showed no elevation of the skin temperature, although a deep cyanotic flush developed. In another group of twelve cases, with the appearance of an intense cyanotic flush, there was no elevation of the skin temperature, but with elevation of the dose, the cyanotic tint changed to bright red and an elevation of the skin temperature appeared. After the injection had been stopped, the flush lasted, although the skin temperature returned to normal. In certain of these cases it was also observed that with the same dose one area might show elevation in skin temperature while others did not. This type of reaction occurred most frequently. A third group (seven cases) always responded to histamine with bright color and an immediate elevation of the temperature.

These observations indicate that histamine produces a dilatation of the venules more regularly than of the arterioles. Dilatation of the venules frequently occurs without simultaneous dilatation of the arterioles. Slight dilatation of the arterial loop of the capillaries was observed only with arteriolar dilatation. That histamine has a predilection for the venules and the small veins is also substantiated by observation of the small visible vessels of the conjunctiva. Histamine produced with regularity a diffuse engorgement of the small veins, resulting in congestion. This congestion appeared promptly with the onset of the injection and disappeared within a few minutes after it ceased. In a number of instances the superficial veins of the arm, especially on the side of the injection, became wider while under the effect of histamine.

Cardiac Output.—A knowledge of the cardiac output is essential to an evaluation of the state of the circulation. The output of the heart was therefore measured in seven young normal adults before and during the administration of histamine, applying the Fick principle

with the modification described by Field, Bock and Gildea.[21] Although this method gives somewhat high values, it was satisfactory for these measurements, which were undertaken to discover alterations in the minute and stroke volumes of the heart. In addition, this procedure gives important information as to the respiratory function of the blood. Seven or more alveolar and mixed venous samples were obtained at each determination. The metabolism was measured by Tissot's method. The amounts of histamine injected during the determination of the cardiac output varied from 0.05 to 0.08 mg. per minute, corresponding to from 3 to 5 mg. per hour.

Following the determination of the cardiac output and other functions of the circulation under basal conditions and during saline infusion, the injection of histamine was started. When the effect of histamine reached its height, usually about fifteen minutes after the onset of injection, measurements of the cardiac output and other factors were repeated. Table 5 presents the results. Figures for heart rate and blood pressure are averages of several measurements. With two exceptions, an elevation of the cardiac output occurred. The average elevation of the cardiac output during the administration of histamine was 1.5 liters per minute. Because of the disproportionate rise in the heart rate there was a tendency for the stroke volume to fall from the average 109 cc. before to 95 cc. during the histamine injection. There was a rise in the basal metabolism, corresponding to the elevation of the cardiac output, to 20 per cent above the basal control observations. The relation between the change in the cardiac output and that in the metabolism was similar to that observed in patients with thyrotoxicosis. The elevation in the carbon dioxide output was less than the corresponding increase in the oxygen absorption in every instance, so that a fall of the respiratory quotient ensued. Considering that the ventilation showed an elevation less than that expected from the elevation of basal metabolism, it would seem that the carbon dioxide, owing to an insufficient increase in ventilation, was not promptly eliminated from the tissues. The fall in the respiratory quotient in these relatively short experiments was more apt to be due to physical alterations between ventilation and blood flow than to a change in the metabolized foodstuffs.

Circulating Blood Volume.—The circulating blood volume of nine subjects was measured by the method of Keith, Rowntree and Geraghty[22] before and during the administration of histamine. In

21. Field, H., Jr.; Bock, A. V.; Gildea, E. F., and Lathrop, F. L.: The Rate of the Circulation of the Blood in Normal Resting Individuals, J. Clin. Investigation **1**:65, 1924.

22. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547 (Oct.) 1915.

TABLE 5.—*The Effect of Continuous Intravenous Administration of Histamine on the Cardiac Output, Respiration and Metabolism*

Observation	Age	Histamine per Min., Mg.		Heart Rate per Min.	Arterial Blood Pressure		Respiratory Minute Volume	Volume of Single Respiration, Cc.	Carbon Dioxide Tension			Carbon Dioxide Output per Min., Cc.	Cardiac Output per Min.	Cardiac Output per Beat, Cc.	Respiratory Quotient	Metabolism, per Cent
					Systolic, Mm. Hg.	Diastolic Mm. Hg.			Alveolar, Mm. Hg.	Venous Virtual, Mm. Hg.	Difference, Mm. Hg.					
1	25		Before histamine	72	100	64	7.0	411	42.4	49.1	6.7	216	7.8	109	0.875	+ 4
		0.07	During histamine	95	106	65	7.4	453	42.5	48.4	5.9	224	9.4	99	0.766	+23
2	..		Before histamine	78	118	70	8.0	381	46.4	51.7	5.3	227	10.6	136	0.832	+12
		0.05	During histamine	97	115	68	9.3	358	45.1	50.4	5.3	229	10.8	111	0.755	+28
3	19		Before histamine	46	104	72	4.8	343	43.0	50.8	7.8	161	5.0	109	0.805	—19
		0.08	During histamine	74	115	65	5.9	368	41.6	47.6	6.0	187	7.7	103	0.719	+ 5
4	10		Before histamine	65	114	80	6.2	476	34.6	45.8	11.2	197	3.9	59	0.777	+ 7
		0.08	During histamine	108	116	76	6.9	460	37.5	46.4	8.9	216	5.4	50	0.750	+30
5	21		Before histamine	57	130	80	7.2	437	44.7	51.4	6.7	239	9.2	160	0.850	+ 3
		0.08	During histamine	80	112	62	8.1	427	43.7	48.8	5.1	248	12.4	155	0.745	+15
6	32		Before histamine	72	106	70	4.8	369	40.3	44.9	4.6	147	7.8	108	0.744	—14
		0.08	During histamine	93	106	64	6.1	468	39.4	45.9	6.5	204	7.4	79	0.683	+30
7	26		Before histamine	83	132	86	5.8	413	43.8	51.5	7.7	222	7.0	84	0.742	+28
		0.07	During histamine	120	129	80	6.2	443	44.3	51.0	6.7	228	8.5	70	0.737	+33

every case the injection of histamine had been going on for at least an hour in sufficient concentration to give marked systemic effects. The subjects were the same as those in whom the cardiac output was measured. Table 6 presents the results of these observations. The blood volume showed no significant change in five persons, a slight increase in two and a moderate decrease in two. The plasma volume showed no important changes in six subjects, and a slight decrease in three. The hematocrit reading was increased in six, slightly decreased in one and unchanged in two.

Metabolism.—In order to ascertain whether or not the described changes in the circulation were associated with changes in the

TABLE 6.—*The Effect of Histamine on the Circulating Blood Volume*

Observation	Histamine per Min., Mg.	Plasma Volume	Blood Volume	Blood Volume, per Cent of Body Weight	Hematocrit Reading	Comment
1	....	2,860	5,085	6.56	43.8	Before histamine
2	0.07	2,860	5,432	7.03	47.4	During histamine
3	....	2,710	5,355	8.52	49.4	Before histamine
4	0.05	2,710	5,370	8.33	49.5	During histamine
5	....	2,825	4,790	7.50	41.0	Before histamine
6	0.08	2,412	4,246	6.63	43.2	During histamine
7	....	2,690	4,485	7.60	40.0	Before histamine
8	0.08	2,520	4,295	7.28	41.4	During histamine
9	....	2,615	4,675	8.22	44.1	Before histamine
10	0.08	2,245	4,075	7.15	45.0	During histamine
11	....	3,425	6,265	7.55	45.4	Before histamine
12	0.08	3,150	6,100	7.35	48.3	During histamine
13	....	2,650	4,675	7.87	43.3	Before histamine
14	0.07	2,750	4,850	8.15	43.3	During histamine
15	....	2,570	4,890	7.43	47.5	Before histamine
16	0.10	2,635	4,845	7.36	45.6	During histamine
17	....	2,930	5,300	8.22	44.5	Before histamine
18	0.10	2,850	5,625	8.72	48.9	During histamine

metabolism, the oxygen consumption observed under basal conditions was compared with that found during the administration of histamine. Two sets of experiments were devised. In one group of subjects the oxygen consumption was followed with the Benedict Roth instrument. After control measurements with and without the injection of saline, increasing amounts of histamine were infused up to the rate of 0.12 mg. for one hour, and the metabolism was measured repeatedly. Control measurements were also performed after the administration of histamine ceased. In all subjects an elevation of the basal metabolism was found, which returned to the original level after the infusion of histamine was stopped. Control infusions of saline produced no changes. Three of the typical experiments are given in table 7. The rate of elevation varied in some instances, reaching as high as 50 per cent. In another group of seven subjects, presented in table 4, the oxygen and carbon dioxide exchange was measured by the Tissot

method. In these cases, again, an elevation was found in every instance. With the same rate of injection, considerable variation was shown in the degree of elevation of the metabolism.

Effect on the Red Cells and White Cells.—In five normal subjects, following the administration of histamine in amounts of from 7 to 10 mg. per hour, the effect on the formed elements of the blood was

TABLE 7.—*The Effect of Histamine on Oxygen Consumption*

Age	Observation	Heart Rate per Min.	Arterial Blood Pressure: Systolic Mg.Hg.	Arterial Blood Pressure: Diastolic, Mg.Hg.	Histamine per Min., Mg.	Oxygen per Min., Cc.	Calories per Hour per Sq. M.	Metabolism, per Cent of Normal	Comment
19	1	68	116	58	....	271	36.2	—12	Control with saline infusion
	2	69	114	60	0.04	272	36.5	—11	
	3	82	110	76	0.08	314	42.1	+ 2.5	
	4	60	112	78	....	270	36.3	—11	Ten minutes after injection of histamine stopped
28	5	71	104	74	....	173	33.3	—16	Control without intravenous infusion
	6	71	106	72	....	165	31.7	—20	Control with saline infusion
	7	90	106	56	0.06	243	46.7	+18	
	8	107	95	50	0.10	341	65.0	+65	
	9	103	110	70	0.10	231	44.4	+11	
	10	86	114	80	....	208	40.1	+ 2	Immediately after injection of histamine stopped
	11	84	96	72	....	206	39.6	0	Five minutes after injection of histamine stopped
	12	80	100	74	....	177	34.0	—14	Fifteen minutes after injection of histamine stopped
40	13	68	116	86	....	256	37.4	— 3	Control without intravenous infusion
	14	68	112	84	....	262	41.3	+ 7	Control with saline infusion
	15	73	110	80	0.01	260	38.2	— 1	
	16	92	128	76	0.06	299	43.7	+14	
	17	104	116	45	0.12	378	55.3	+43	
	18	106	116	50	0.12	408	59.6	+55	
	19	72	108	74	....	271	39.7	+ 3	Ten minutes after injection of histamine stopped
	20	66	112	84	....	278	40.7	+ 6	Twenty minutes after injection of histamine stopped

studied. Blood specimens obtained immediately before and ten minutes and one hour after the injections of histamine were started were compared. The number of the red and white cells was counted. Blood smears for changes in the morphology of the red cells and white cells were studied. No definite alterations in the cells and the platelets were observed. The red cells, reticulocyte counts and hemoglobin content showed no changes. The number of white cells increased in all cases during the administration of histamine. The number of the polymorphonuclear leukocytes increased, and the lymphocytes decreased in four of five cases. The fifth case had a high monocyte

TABLE 8.—*The Effect of Histamine on Certain Chemical Constituents and Physical Characteristics of the Blood* *

Observation	Histamine per Hour, Mg.	Dextrose			Nonprotein Nitrogen			Sodium Chloride			Freezing Point			Protein			Specific Gravity		
		Before Histamine	After Histamine	Difference	Before Histamine	After Histamine	Difference	Before Histamine	After Histamine	Difference	Before Histamine	After Histamine	Difference	Before Histamine	After Histamine	Difference	Before Histamine	After Histamine	Difference
1	6	97	113	+16	32	30	−2	587	603	+13	0.583	0.579	−0.004	6.79	6.60	−0.19	1.0263	1.0255	−0.0008
2	6	87	99	+12	24	24	0	590	590	0	0.567	0.578	+0.011	6.77	6.58	−0.18	1.0257	1.0252	−0.0005
3	7	107	127	+20	31	31	0	587	572	−15	0.562	0.605	+0.043	6.97	7.34	+0.37	1.0270	1.0275	+0.0005
4	7	104	133	+29	31	29	−2	589	598	+ 9	0.575	0.577	+0.002	7.28	7.03	−0.25	1.0268	1.0261	−0.0007
5	8	83	86	+ 3	21	20	−1	595	594	− 1	0.562	0.543	−0.019	6.20	6.20	0.00	1.0249	1.0248	−0.0001
6	12	83	94	+11	23	23	0	580	573	− 7	0.563	0.551	−0.012	7.19	7.10	−0.09	1.0261	1.0261	−0.0000

* All values, with the exception of the specific gravity and freezing point, indicate the contents in 100 cc. of blood.

count throughout. There was some increase in the platelet count, and the venous blood obtained during the administration of histamine showed many clumps of platelets. Because of the small number of cases studied and the lack of definite changes, we refrain from drawing conclusions from these observations.

The Chemical Constituents of the Blood.—Because of the alleged rôle of histamine in surgical shock, in which condition appreciable concentration of the blood occurs, a number of constituents and characteristics of the blood such as the dextrose, nonprotein nitrogen, sodium chloride, protein, freezing point and specific gravity were measured in six subjects before and after the administration of histamine for one or two hours at a rate of from 5 to 12 mg. per hour.

Although the effect of histamine was manifested in all of these cases by rapid heart rate, intense scarlet flush, nausea and severe headache,

TABLE 9.—*The Effect of the Continuous Infusion of Histamine on the Lactic Acid Content of Blood*

Experiment	Age	Histamine, Mg. per Hour	Effect of Histamine Infusion on Lactic Acid, Mg. per 100 Cc.			Source of Blood
			Control	After 10 Min.	After 60 Min.	
1	52	8	11.6	11.0	10.8	Femoral vein
2	50	7	14.0	16.4	11.6	Cubital vein
3	30	7	26.3	20.1	25.2	Cubital vein
4	..	10	14.1	17.0	17.7	Cubital vein
5	29	7	16.5	15.5	14.2	Cubital vein

as indicated in table 8, no appreciable change in the blood constituents could be detected. The average amount of saline solution injected was 30 cc. per hour. The freezing point of the salt solution used varied between Δ 564 and 568. It is hardly probable that the addition of this amount of saline through a relatively long time exerted a significant diluting effect on the blood and hence obscured the changes produced by histamine.

In another five subjects, the influence of histamine on the lactic acid content of the blood was investigated.[23] Histamine was administered for one hour, and the lactic acid content was measured, as indicated in table 9, before and ten and sixty minutes after the injection of histamine was started. The results of these measurements indicate that the administration of histamine fails to influence definitely the lactic acid content of the blood.

Although measurements of the constituents described failed to indicate any increased concentration of the blood, the average oxygen capacity of the arterial blood in seven subjects in whom the blood

23. Friedemann, T. E.; Cotonio, M., and Shaffer, P. A.: The Determination of Lactic Acid, J. Biol. Chem. **73**:335, 1927.

gases were studied rose from 22.1 per cent by volume to 23.7 per cent by volume. The degree of rise was similar in every case. The details of these observations will be reported elsewhere.

Respiration.—It was observed previously [18] that attacks may be precipitated in patients subject to bronchial and cardiac asthma by the administration of small amounts of histamine. Associated with this reaction, there is a reduction of vital capacity, and this, together with a lowered position of the diaphragm and the appearance of bronchi, suggests bronchial constriction. This assumption is further substantiated by the observation that epinephrine promptly relieves asthmatic attacks precipitated by histamine.

This behavior of patients with bronchial and cardiac asthma raises the significant problem as to whether normal persons respond with a similar respiratory embarrassment of lesser degree, or whether in asthmatic patients one is dealing with an altered reaction to histamine. The vital capacity of ten normal subjects was measured before and during the height of the histamine reaction. No change was observed. Graphic representation of the respiration also failed to show change in the rate or depth of the respiration, even when such large amounts as 10 mg. of histamine were administered per hour. These findings, together with the comparative respiratory minute volume studies included in table 4 and the lack of changes in the respiratory breath sounds and any complaints of dyspnea in normal persons, indicate that up to toxic doses histamine in normal persons fails to produce bronchial constriction or any other type of respiratory embarrassment. These observations, therefore, establish the fact that patients with asthma react not with increased sensitivity but with an altered response (idiosyncrasy) to histamine.

THE EFFECTS OF SUBCUTANEOUSLY ADMINISTERED HISTAMINE ON THE CARDIAC RATE AND BLOOD PRESSURE IN MAN

Although the effect of subcutaneously administered histamine has been studied before, in order to compare the systemic as well as the cardiovascular effect of subcutaneously administered histamine with that of intravenously administered histamine, a few observations were made on the effect of the subcutaneous administration of histamine on the cardiac rate and arterial blood pressure. Ten young adults, after a control period of observation, were given 0.5 mg. of histamine, and the effect on the cardiac rate, blood pressure and cutaneous vessels was observed. Both the systolic and the diastolic blood pressure showed a slight but transient fall, although this again was not observed in every instance. The cardiac rate per minute usually showed a maximal elevation of from 10 to 20 beats for from three to five minutes, after which

it returned to normal. The maximum intensity of the flush and the subjective reactions corresponded in general to the continuous intravenous injection with a rate of from about 0.03 to 0.05 mg. per minute. In three cases doses of both 0.5 and 1 mg. were administered at different times, and while a temporary slight fall in the systolic and diastolic pressure was observed after 0.5 mg., no change in the blood pressure was noted following 1 mg., although the elevation of the pulse rate was greater and of longer duration.

THE EFFECT OF ORALLY ADMINISTERED HISTAMINE ON MAN

Five normal volunteer subjects received gradually increasing amounts of histamine up to from 200 to 500 mg. No subjective or objective changes were observed. The pulse rate and the arterial blood pressure remained unaltered. Considering the massive doses administered, it may be concluded that histamine fails to produce any subjective effect or any changes in the cardiovascular system when administered in unusually large amounts orally.

COMMENT

The Sensitivity and Tolerance of Man to Histamine.—The minimal single intravenous injection of histamine that exerts changes in the cerebral or facial blood vessels and the cardiac rate is 0.02 mg. of histamine phosphate, corresponding to 0.007 mg. of histamine base, while the maximal injection that can be tolerated and will produce a marked circulatory response with mild toxic manifestation is from 0.2 to 0.3 mg. On one occasion, the sudden injection of 1 mg. of histamine given by mistake, produced alarming symptoms for a few minutes. Changes due to the direct effect of histamine on the cardiovascular system last only from forty to eighty seconds as a rule, although some of the sequelae of these changes, such as headache, may persist longer.

A comparison of the sensitivity of the human and animal circulations to histamine is obviously difficult because of difference in the pharmacologic effect and experimental conditions. The fact that dogs, following the injection of 0.0054 mg. per minute per kilogram, show an intense toxic reaction (Koessler and Hanke[24]) and that human subjects tolerate 0.004 mg. (histamine phosphate) per minute per kilogram, with an intense response but no alarming manifestations, suggests that the relative tolerance is essentially not different in dog and in man. Such small doses as 0.001 mg., given intravenously, produce a definite fall in the arterial blood pressure of the anesthetized cat (Feldberg[9]), while 0.1 mg. of histamine phosphate, corresponding to 0.03 mg. of the base,

24. Koessler, K. K., and Hanke, M. T.: The Intestinal Absorption and Detoxication of Histamine in the Mammalian Organism, J. Biol. Chem. **59**:889, 1924.

produces a definite but not a toxic response in man. From these responses to various dosages it is fair to assume that the susceptibility of man to histamine is not out of proportion to that of the higher mammals.

The rate of the entrance of histamine into the circulation is of fundamental importance in determining the intensity of the effect of histamine on the human cardiovascular system. The fact that an even rate of injection of histamine into the human circulation produces in general a uniform intensity of response, regardless of the duration of the injection, indicates that histamine is promptly converted into inert substances in the human body. The experiments presented also indicate that man tolerates, and hence is capable of destroying, as much or more than 20 mg. of histamine in an hour, although one two-hundredths of this amount produces an intense reaction when injected suddenly. In this respect, the human body behaves similarly to that of the rabbit, as observed by Oehme.[25] Although the evidence presented indicates that histamine becomes inert promptly after it enters the human circulation, the observations do not reveal the nature of its inactivation. The fate of histamine in the body is practically unknown. Intracutaneously injected histamine is not destroyed locally if the circulation is stopped by the application of a tourniquet. This suggests that all the tissue cells do not possess the ability to destroy histamine. Our experience suggests further that the blood is not the seat of the inactivation of histamine in man. Patients with cardiac decompensation, with a three to four-fold decrease in the velocity of the blood flow, are no less sensitive to histamine than persons with a normal circulation.

The fact that the minute blood vessels respond promptly but fleetingly to a single intravenous dose of histamine is weighty evidence that histamine is destroyed in the endothelial surface of the vascular wall. This conception is supported by two independent observations previously not fully understood by us.[13] Patients with emphysema show an increased peripheral vascular response to histamine, while in patients with hyperthyroidism the response is of less than normal intensity. In emphysema the capillary bed of the lungs is considerably decreased, while in hyperthyroidism, with the increased cardiac output, the surface of the pulmonary capillary bed is probably increased. All these observations point to the endothelial system of the vascular tree, and especially to the lungs, as important to the inactivation of histamine in man. Best [26] rather recently reported that the autolyzed lung tissue

25. Oehme, C.: Ueber die Wirkungsweise des Histamins, Arch. f. exper. Path. u. Pharmakol. **72**:76, 1913.

26. Best, C. H.: The Disappearance of Histamine from Autolyzing Lung Tissue, J. Physiol. **67**:256, 1929.

is capable of destroying considerable amounts of histamine. This action of the lung tissue, according to Best, possesses some of the characteristics of an enzyme. Liver and kidney in vitro also destroy histamine. Best did not determine the nature of the destruction of histamine by these tissues.

The fact that the oral administration of such large amounts of histamine as 500 mg. fails to exert any appreciable influence on the cardiovascular system in man, and that such small amounts as 0.05 mg. per minute in the blood stream exert a definite systemic effect, would suggest that histamine, taken internally, is inactivated before it reaches the general circulation. Two explanations are open: Either histamine is inactivated by a special function of the intestines before it enters the portal circulation, or it is destroyed by the liver before it enters from the portal to the greater circulation. Considering that in animals it has been shown repeatedly that the liver does not inactivate histamine to any extent (Popielski,[27] Koessler and Hanke [24] and Ivy and Javois [28]), it seems probable that the human intestine, like that of animals, possesses a special capacity to destroy this substance. These observations in adults make questionable the validity of the theory that histamine is an important factor in "intestinal intoxication," as was suggested by the observations of Eppinger and Gutmann,[29] Mellanby,[30] Röthler [31] and Roske.[32] Such doubt can be disproved only by the demonstration of a decreased detoxicating or increased absorptive power of the intestines in patients with "intestinal intoxication."

In certain species of animals, under certain experimental conditions, histamine administered orally may enter the blood stream in sufficient concentration to induce changes in the circulatory mechanism (Meakins and Harington [33]).

---

27. Popielski, L.: B-Imidazolyläthylamin und die Organextrakte: I. B-Imidazolyläthylamin als mächtiger Erreger der Magendrüsen, Arch. f. d. ges. Physiol. **178**:214, 1920; II. Einfluss der Säuren auf die Magensatsekretion erregende Wirkung der Organextrakte, ibid. **178**:237, 1920.

28. Ivy, A. C., and Javois, A. J.: The Stimulation of Gastric Secretion by Amino Acids and Amines, Am. J. Physiol. **68**:132, 1924; Contributions to the Physiology of Gastric Secretions: VI. The Stimulation of Gastric Secretion by Amines and Other Substances, ibid. **71**:604, 1925.

29. Eppinger, H., and Gutmann, J.: Zur Frage der vom Darm ausgehenden Intoxikationen, Ztschr. f. Klin. Med. **78**:399, 1913.

30. Mellanby, E.: An Experimental Investigation on Diarrhoea and Vomiting of Children, Quart. J. Med. **9**:165, 1916.

31. Röthler, H.: Ueber das Verhalten der Amine bei Dyspepsie und Intoxikation, Jahrb. f. Kinderh. **120**:162, 1928.

32. Roske, G.: Ueber Bedingungen der Aminbildung durch Bact. coli, Jahrb. f. Kinderh. **120**:186, 1928.

33. Meakins, J., and Harington, C. R.: The Relation of Histamine to Intestinal Intoxication: I. The Presence of Histamine in the Human Intestine, J. Pharmacol. & Exper. Therap. **18**:455, 1922.

Certain observations made in this study show that besides the chemical inactivation of histamine in man there is also a physiologic inactivation through the formation of a substance or substances antagonistic to histamine. It was frequently observed that if the infusion of histamine was continued for several hours, not only was there no accumulation of effect, but, on the contrary, the intensity of the response of the cardiovascular system gradually decreased. Often the mottled pale skin island within the flushed areas progressively increased, and the degree of elevation of the cardiac rate decreased. Furthermore, with cessation of the infusion there was a definite rise in the systolic, and especially in the diastolic, arterial blood pressure as compared with the normal control level, and the skin appeared remarkably pale. These observations suggest the production of an antagonistic substance in man as a response to the prolonged effect of histamine, a concept postulated on the basis of entirely different observations by Lewis [3] and Burn and Dale.[2] This hypothetic substance, although similar in its action to epinephrine, may be another vasoconstrictor substance. A second possibility, that this physiologic inactivation of histamine does not occur through chemical antagonism, but rather as an antagonistic response of the vasomotor nervous system, cannot be ruled out at present.

The Response of the Cardiovascular System.—During the intravenous infusion of histamine at rates up to toxic doses such as from 10 to 20 mg. per hour, the observed responses of the human circulation may be summarized as follows. The cardiac rate shows a progressive rise to a rate as high as from 130 to 140. Simultaneously, there is a moderate increase in the cardiac output. The circulating blood volume shows no appreciable change after the infusion of an average dose of 6 mg. of histamine in one hour. The blood, however, as judged from the increased oxygen combining power, shows an increased concentration of hemoglobin, although the chemical constituents of the plasma remain unaltered. This indicates a transudation of small amounts of the blood plasma into the tissues. Because the circulating blood volume decreases slightly, the mean velocity of blood increases. The calculated mean circulation time was forty-two seconds before the administration of histamine and thirty-five seconds at the height of histamine effect, one hour after the onset of histamine injection, as was indicated in a previous report.[34] Because the cardiac output is not proportional to the elevation of the heart rate, the stroke volume of the heart under the effect of histamine decreases slightly. The metabolic rate is accelerated, and the cardiac output increases about proportionately with the metabolism.

34. Weiss, S.; Ellis, L. B., and Robb, G. P.: Bodily Responses in Man During the Continuous Intravenous Administration of Histamine, Am. J. Physiol. **90**:551, 1929.

Although the minute cerebral and cutaneous blood vessels show dilatation, the blood pressure as a rule is not lowered appreciably. In a number of instances a moderate lowering of the diastolic pressure was noted. The venous pressure was unaltered or slightly elevated.

The most significant of these findings is that man does not as a rule respond to histamine with a prompt fall in arterial blood pressure. One of the factors responsible for this maintenance of a sustained arterial pressure is that the peripheral dilatation of the minute vessels in man, in response to intravenous infusion of histamine, is not general. Whether other vascular areas besides the skin and the brain also respond with prompt dilatation is questionable. Amounts that produced dilatation of the minute vessels of the brain and of the skin failed to produce dilatation of the minute vessels of the abdominal organs in patients in whom laparotomy was performed under spinal anesthesia. Even in the skin vessels, the dilatation is more apt to occur in the venules than in the arterioles. But even if there is an increased blood flow through the skin, the pressure in the minute vessels is not appreciably elevated, indicating only a relatively slight arteriolar dilatation as compared with the dilatation that follows the direct intracutaneous injection of histamine (Ellis and Weiss [35]).

The second factor that prevents the lowering of the blood pressure is the prompt response of the heart with a moderately increased output. There is no decrease, but, on the contrary, an increase in the venous return of the blood to the right side of the heart in man in response to histamine. This behavior of the human heart is contrary to that of the cat's heart, which according to Dale and Laidlaw,[7] shows a decreased systolic output due to a decreased venous return and not to primary cardiac weakness. Rühl [36] reported recently that the decreased cardiac output in dogs is mainly due to damage of the myocardium. However, the doses given by Rühl were unusually large. Changes in the complexes of the electrocardiogram indicate that in man histamine exerts a direct action on the coronary circulation or the myocardium even when administered in relatively small amounts. The more exact mechanism of this action of histamine on the human heart is not clear.

The demonstration of the unusual sensitivity of the human cerebral blood vessels is especially significant. Not only do the observations demonstrate that the minute vessels of the human brain are capable of responding promptly with alteration in their diameter, but quantita-

35. Ellis, L. B., and Weiss, S.: The Measurement of Capillary Pressure Under Natural Conditions and After Arteriolar Dilatation: In Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, J. Clin. Investigation **8**:47, 1929.

36. Rühl, A.: Ueber Herzinsuffizienz durch Histamin, Arch. f. exper. Path. u. Pharmakol. **145**:255, 1929.

tive evaluation of these responses suggests that histamine and perhaps other substances through their local action may play a rôle in the regulation of the cerebral circulation in man.

The great capacity of the human capillary venules up to the visible smaller veins to respond independently of the arterioles has also been clearly demonstrated. Such dilatation of the venules over a large area may shunt and shift considerable amounts of the blood volume. Thus one effect of the injection of histamine may be the shunting of a part of the circulating blood into one area, where the blood flow becomes relatively slow; in other areas, at the same time, it may be increased because of arteriolar dilatation. In our experience the dilation of the cutaneous venules with different dosages occurs more regularly than the dilatation of the arterioles.

We wish to emphasize here, once more, that the effect of histamine on the minute vessels and on the circulation as a whole, when introduced into the blood stream, does not necessarily bear on the alleged rôle of histamine between cell function and local capillary activity.

Histamine and Muscular Exercise.—A number of the bodily responses of the cardiovascular system observed in man following the administration of histamine are similar to a certain extent to those that occur during and immediately following exercise. Increased cardiac rate, metabolism, velocity of blood flow and cardiac output are common physiologic characteristics of both exercise and histamine effect. The degree of the changes mentioned was less following the infusion of histamine than after exercise when related to the elevation of the cardiac rate. Furthermore, dyspnea may be intense in patients with circulatory failure following the administration of histamine, although in normal subjects this has not been observed even if the amount of histamine administered was sufficiently high to produce such a high cardiac rate as is observed only after intense muscular exertion associated with dyspnea. The lactic acid content of the blood failed to show any definite elevation during the histamine effect in contrast to muscular exercise. These facts, therefore, indicate that the analogy between the circulatory responses due to histamine and muscular exercise is only partial. The essential similarity is that histamine infusion, like muscular exercise, represents a burden on the human circulation.

Respiration and Pulmonary Circulation.—Study of various aspects of the respiration indicates that histamine produces no appreciable constriction of the bronchiolar tree in normal man. Since elevation in the intrapulmonary pressure, as well as increased pressure in the pulmonary artery, often reflects itself in changes in the venous pressure, the finding of unaltered or slightly elevated venous pressure together with the maintenance of a normal respiratory mechanism is evidence that hist-

amine up to toxic doses produces no marked constriction of the bronchioles or the minute vessels of the pulmonary circuit. On the other hand, in patients with bronchitis, bronchial asthma and certain forms of cardiac asthma, small amounts of histamine may induce bronchial and vascular constriction with an increase in the venous pressure. This suggests an altered response of the pulmonary system to histamine in these conditions, and the observations have an important bearing on the mechanism of anaphylaxis.

Histamine and Traumatic Shock.—Dale and Laidlaw,[7] in analyzing the effect of the continuous intravenous administration of histamine on anesthetized cats, observed that the circulatory responses in many respects are analogous to those observed in man in traumatic shock. An investigation of the nature of the histamine shock observed revealed that the observed cardiac failure and lowered blood pressure are results of an insufficient venous return, which is caused by stagnation of the blood in the capillaries and venules throughout the body, thus depleting the large arteries and veins. It is these circulatory characteristics that are most significant in shock. The increased hemoglobin content, which results from transudation of the whole plasma into the tissues, is considered by these authors not an essential, but a contributory, factor in the development of histamine shock. Hashimoto [37] confirmed the findings of Dale and Laidlaw that histamine increases the hemoglobin content of the blood without increasing the total solids of the plasma. Underhill and Kapsinow,[38] however, failed to observe an increased concentration of the blood if their dogs received a sufficient amount of water before the experiment. Similarly, in rabbits, Underhill and Roth [39] found no concentration of the blood induced by histamine. These apparently contradictory results are of great significance for, as pointed out, the capillary systems of different species reacts differently to histamine, and therefore it is easily probable that shock phenomena observed in cats may not be present in other animals.

Our observations on man revealed, in accordance with the findings of Dale and Laidlaw in the cat, a slight but definite increase in the hemoglobin content of the blood during the injection of histamine without any change in the protein, total solids or freezing point of the plasma. This indicates that under the influence of histamine the capil-

37. Hashimoto, H.: Blood Chemistry in Acute Histamine Intoxication, J. Pharmacol. & Exper. Therap. **25**:381, 1925.

38. Underhill, F. P., and Kapsinow, R.: The Influence of Water Deprivation upon Changes in Blood Concentration Induced by Experimental Shock, Am. J. Physiol. **63**:142, 1922.

39. Underhill, F. P., and Roth, S. C.: The Influence of Water Deprivation, Pilocarpin, and Histamine upon Changes in Blood Concentration in the Rabbit, J. Biol. Chem. **54**:607, 1922.

laries of man permit the whole plasma to pass from the blood into tissues, spaces or lymphatics. In man, the amount of plasma that left the blood stream after the administration of from 6 to 10 mg. of histamine in an hour must have been small, about 6 or 7 per cent of the normal plasma volume, as may be estimated from an increase in percentage of the hemoglobin combining power. The amount of plasma that left the blood stream was too small to have been demonstrable by the measurement of the blood volume by the dye method. The finding of an increased concentration of the blood due to transudation of plasma into the tissues does not indicate that the reaction of man to histamine is similar to that of anesthetized cats. This change, as also stated by Dale and Laidlaw, is not the characteristic feature of shock.

The important question as to whether or not man responds to histamine with a tendency to develop shock cannot be answered definitely from the observations presented. There are several significant findings, however, that strongly suggest that in normal subjects histamine does not induce a shocklike condition. If histamine is infused slowly and continuously into the circulation of the cat, the blood pressure falls promptly, even from small doses. This fall in pressure is early associated with a decreased cardiac output due to a decreased venous return and stagnation of a considerable amount of blood in the capillary system. These changes, which form the fundamental features of shock in cats, are not observed in man, even when such large amounts as from 10 to 20 mg. of histamine are administered per hour for as long as two hours. In man, the arterial pressure does not fall, or the fall is but slight and venous pressures do not decrease, hence a depletion of the large arteries and veins does not occur. The cardiac output and the mean velocity of blood flow are not decreased but rather elevated, although small amounts of blood may occasionally stagnate in the cutaneous tissues. Even here, in many instances, the blood flow is increased. Evidence is lacking, therefore, that in man histamine acts as a generalized capillary depressant in doses that are capable of inducing marked systemic effects and of elevating the cardiac rate as high as 140 per minute. The elevated basal metabolism is also contrary to the reaction characteristic of experimental shock.[40]

Objection may be made to this argument by supposing that higher doses than those applied in this study might induce the responses of shock. Such a possibility cannot be denied; however, considering the intensity of the general symptoms induced by the dosage applied and the absence of any observable tendency to shock, it is questionable if this objection is valid.

40. Aub, J. C.: Studies in Experimental Traumatic Shock: I. The Basal Metabolism, Am. J. Physiol. **54**:388, 1920.

Even if higher toxic doses of histamine did induce characteristic shock in man, the argument that shock is due to a liberation and accumulation of histamine in the blood stream would not be supported. Such a response could not be considered as specific, as it is observed with numerous chemical agents when given in toxic doses.

Although Cannon [8] offered evidence in support of the theory that traumatic shock is induced by a chemical substance, possibly histamine, it must be remembered that the changes in the minute blood vessels in shock are not characteristic of the effect of any single substance. A number of different chemical and physical agents might precipitate shock with identical circulatory changes; as Dale and Laidlaw [7] rightly emphasized, "The existence of these points of community, in the action of substances so utterly unrelated chemically as histamine and certain metallic ions, forbids any assumption that the production of similar effects, by unknown constituents of some organ or tissue, indicates the presence therein of histamine itself, or of any substance chemically related to it. The similarity depends on the fact that all act on the endothelium and produce in it changes probably of the same general type." Recent evidence rather supports the concept that in traumatic shock the damage of the minute blood vessels is due to a progressive depression of the peripheral vasomotor mechanism. This may often occur without the presence of histamine or other chemical substances. The difference in degree of the relative susceptibility of the augmentor and inhibitory fibers to certain stimuli explains the depressor vascular responses of shock.[41] These facts and our failure to reveal any specific tendency on the part of histamine to induce shock in man do not support the theory that histamine is essential to or responsible for traumatic shock in man.

SUMMARY AND CONCLUSIONS

1. A study of the systemic effects of histamine in man and a discussion of the physiologic and pathologic rôle of histamine, based on these observations, are presented.

2. Following the single or continuous intravenous administration of histamine, the latter is converted promptly into ineffective substances in the human body. The persistence of the action of histamine in man is of but a few minutes' duration. With uniform intravenous infusion, the bodily changes induced are practically stationary.

3. The minimal effective amount of histamine base in man is about 0.003 mg. per minute, corresponding to a concentration of about

41. Smith, M. I.: Studies on Experimental Shock with Especial Reference to Its Treatment, J. Pharmacol. & Exper. Therap. **32**:465, 1928; The Peripheral Vasomotor Mechanism in Experimental Shock, ibid. **34**:239, 1928.

1:2,000,000,000 parts in the circulating blood. The maximal amount of histamine base, administered intravenously, that produces toxic manifestations is 0.15 mg. per minute.

4. The symptoms and signs of histamine intoxication in man are described.

5. Relatively small amounts of histamine (0.003 mg. per minute) cause a depression of the T waves of the complexes of the normal electrocardiogram. With elevation of the dosage, the degree of depression increases, until the T wave may become inverted. After a single intravenous dose, the change in the shape of the T wave is instantaneous with the arrival of histamine in the coronary circulation, and within one minute there is a tendency to return to the normal shape. Changes in the T waves are not associated with any symptoms or signs referable to the heart.

6. Histamine in amounts up to toxic doses in observations of two hours' duration fails, as a rule, to produce any lowering of the systolic arterial blood pressure. The diastolic arterial blood pressure shows a tendency to fall, but in numerous instances it also remains unaltered. With increasing amounts, there is a progressive rise in the cardiac rate.

7. The venous pressure is either unaltered or slightly elevated.

8. The effect of histamine on the cutaneous blood vessels is not uniform. The most characteristic effect is a dilatation of the venules and small veins. This effect is frequently independent of the dilator effect on the arterioles. In one group of subjects, even toxic doses fail to produce a dilatation of the arterioles as judged by the cyanotic flush and lack of elevation of the surface temperature of the skin. In a second group of subjects, the arteriolar dilatation develops when a larger dose, rather than one that produces a dilatation of the venules, is administered. In a third group, the dilatation of the arterioles and venules occurs simultaneously.

9. As judged from the degree of elevation of the pressure in the minute vessels of the skin, the arteriolar dilatation following large intravenous doses of histamine is slight as compared with that following the local intracutaneous application of histamine base in a solution of 1:3,000.

10. The different types of observations presented offer conclusive evidence that the minute cerebral vessels of man respond to histamine with conspicuous dilatation. A certain parallelism exists between the sensitivity of the facial and the cerebral vessels to histamine. In a number of instances the cerebral vessels were even more sensitive than the facial vessels, and cerebral arteriolar dilatation followed the intravenous administration of such small amounts as 0.003 mg. of histamine base.

11. The cardiac output per minute following the intravenous infusion of from 0.02 to 0.03 mg. of histamine base per minute increases by an average of 1.5 liters, or to 20 per cent above the normal value. Simultaneously, there is a slight fall in the stroke volume. The mean velocity of blood flow shows a slight but distinct increase.

12. The basal metabolism becomes elevated and may reach values 50 per cent above the normal. There is a slight fall in the respiratory quotient.

13. A study of the chemical constituents and certain physical characteristics of the blood, together with its hemoglobin combining power, indicates that with the administration of histamine, transudation of small amounts of whole plasma occurs. This amount is too small to be demonstrated by the measurements of the total blood volume with the dye method.

14. Histamine produces no demonstrable changes in the pulmonary ventilation or in the state of the bronchioles of normal persons, but has a definite bronchial constrictor effect on patients with bronchitis, bronchial asthma, emphysema and cardiac asthma.

15. Histamine, when administered orally in massive doses, is ineffective; hence, its rôle in intestinal intoxication is highly questionable.

16. Evidence is presented that during the administration of histamine substances are formed or vasomotor reflexes develop which act antagonistically to histamine.

17. The degree of peripheral vascular dilatation in man induced by histamine is not marked, and the distribution is not widespread. The vasodilator effect of histamine is promptly counteracted by an increase in the cardiac output and in other regulatory functions.

18. A certain parallelism exists between the circulatory responses that follow exercise and those that follow the injection of histamine, but this parallelism is incomplete.

19. The vascular and other bodily responses induced by histamine in man differ fundamentally from those observed in anesthetized cats and in patients with traumatic shock. The rôle of histamine in traumatic shock is therefore considered doubtful.

AVITAMINOSIS

IV. THE EFFECT OF A DEFICIENCY OF THE VITAMIN B COMPLEX ON THE LIPID METABOLISM AND GLYCOGEN CONTENT OF THE LIVER OF THE ALBINO RAT *

BARNETT SURE, PH.D.
AND
MARGARET ELIZABETH SMITH, M.S.
FAYETTEVILLE, ARK.

In previous communications we have demonstrated that the main biochemical changes in the albino rat suffering from a deficiency of the vitamin B complex are anhydremia associated with a disturbance in hematopoietic function [1] and, in uncomplicated vitamin B deficiency, a marked reduction in the glycogen content of the liver.[2] Since in such avitaminosis the most pronounced symptom complex is anorexia, the tentative conclusion made was that the pathologic changes encountered may have been, at least in part, produced indirectly through a reduction in food consumption. In this and in the communication following, experimental evidence is submitted on studies carried out by a method which eliminated the plane of nutrition as a complicating factor. Weaned albino rats, weighing from 50 to 60 Gm. and about 4 weeks of age, were transferred from our stock diet 1 [3] to diet 1751, satisfactory in every respect, with the exception of vitamin B complex, and of the following composition: casein,[4] 20; salts, 185; [5] casein, 4; butterfat, 10, and dextrin, 66. Littermates of the same sex were restricted to the same daily water and food intake of that diet, but received in addition an abundance of the vitamin B complex by the replacing of 10 per cent of the dextrin in ration 1751 with dried baker's yeast. Since the plane of nutrition was controlled, the difference in physiologic and pathologic results obtained in these two groups of animals must be attributable to

* Submitted for publication, June 27, 1931.

* Research paper no. 205, Journal Series, University of Arkansas.

* From the Departments of Agricultural Chemistry and Home Economics, University of Arkansas.

1. Sure, B., and Smith, M. E.: J. Biol. Chem. **82**:307, 1929. Sure, B.; Kik, M. C., and Walker, D. J.: ibid. **82**:287, 1929.
2. Sure, B., and Smith, M. E.: Proc. Soc. Exper. Biol. & Med. **27**:861, 1930.
3. Sure, B.: J. Biol. Chem. **69**:65, 1926.
4. Purified by extraction for ten days with acidulated water.
5. McCollum, E. V., and Simmonds, N.: J. Biol. Chem. **33**:63, 1918.

the specific influence of the vitamin B complex. Employing such technic, it became apparent that in this avitaminosis there is produced a lipemia, characterized by a rise in the fatty acids, cholesterol and lecithins of the blood; also that there is a considerable reduction in the glycogen content of the liver.

The blood was obtained by peripheral bleeding according to the technic previously described.[6] For the various determinations of lipids, even employing micromethods, 1 cc. of blood was found necessary. Such an amount of blood represented a large proportion of the total volume of the small avitaminotic animals that were losing weight. Therefore, in

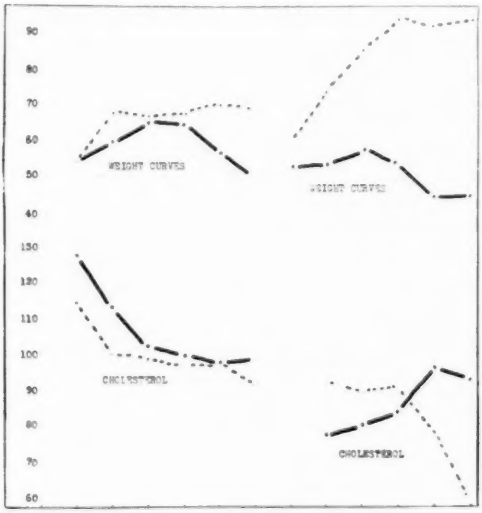

Chart 1.—Weight and cholesterol curves for groups 1938-1939 (left) and 1966-1967 (right). In this and the following charts the heavy line indicates the pathologic group and the dotted line the control group. Each division on the horizontal scale indicates one week. Body weights are expressed in grams.

order to avoid any accompanying anemia that might be precipitated by such a procedure, the blood was pooled from two littermates of the pathologic group, and at the same time samples were taken from two littermate controls. Of 1 cc. one-half was used for the cholesterol determination and the other half for the analyses of lecithin, fatty acids and the iodine number, the latter giving an index of the unsaturated fatty acids. The cholesterol was determined by the Lieberman and

6. Sure, B.; Kik, M. C., and Walker, D. J.: J. Nutrition **1**:299, 1929.

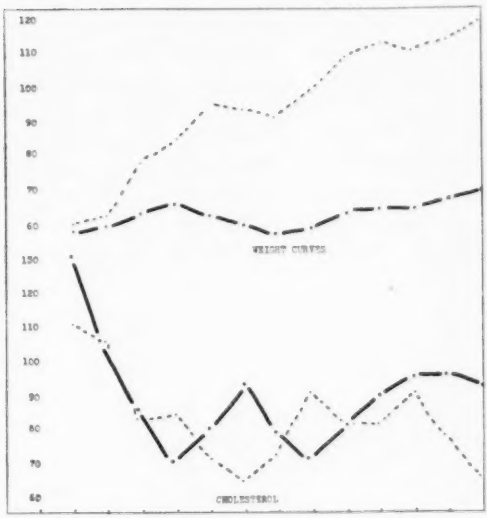

Chart 2.—Weight and cholesterol curves for group 1940-1941. Each division on the horizontal scale indicates one week.

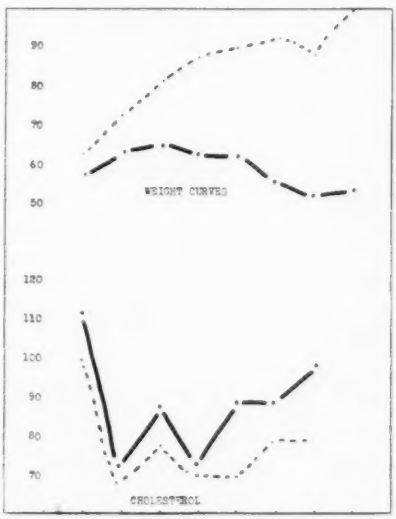

Chart 3.—Weight and cholesterol curves for group 1966-1967. Each division on the horizontal scale indicates one week.

Burchard method,[7] the lecithin by the Fiske and Subbarow method [8] and the fatty acids by the methods of Bloor, Pelkan and Allen [9] and Stoddard and Drury.[10] One modification was found helpful in the determination of fatty acids. They were titrated in a benzene solution with two-hundredth-normal potassium hydroxide made with absolute alcohol.

At the termination of the experiment the animals were killed and the glycogen of the livers was analyzed by a modified method of Pflueger used by Cori and Cori.[11]

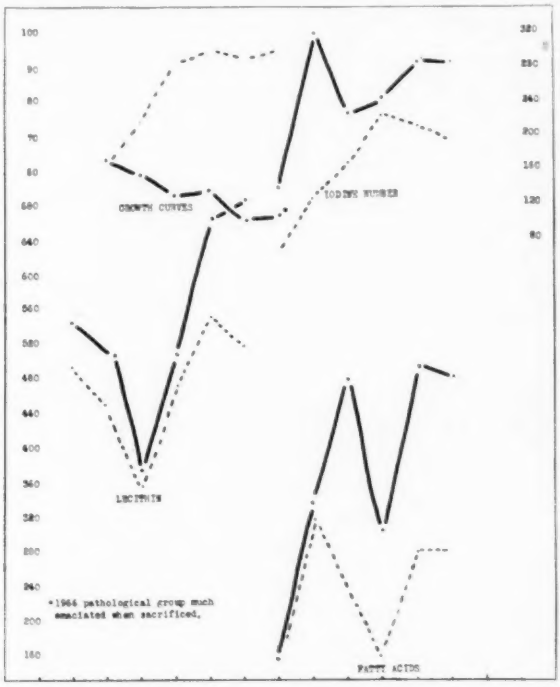

Chart 4.—Curves of growth, iodine number, lecithin and fatty acids for group 1966-1967. Each division on the horizontal scale indicates one week.

The results are presented in charts 1 to 6, inclusive, and in tables 1 and 2.

---

7. Hawk and Bergeim: Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Company, p. 281.
8. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**:375, 1925.
9. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: J. Biol. Chem. **52**:191, 1922.
10. Stoddard, J. L., and Drury, P. A.: J. Biol. Chem. **84**:741, 1929.
11. Cori, D. F., and Cori, G. T.: J. Biol. Chem. **70**:557, 1926.

The weight curves shown in all the charts represent the average growth of two littermates of the same sex. Similarly, the curves showing the concentration of the various lipid constituents of the blood indicate the average figures for two littermate rats of the same sex. This is true of the curves for the control animals (shown in dotted lines) and the pathologic animals (drawn in heavy lines).

It is quite clear from all the charts that, since the plane of nutrition was controlled, the vitamin B complex per se, furnished by dehydrated baker's yeast, produces a considerable effect on growth. Some groups in as short an interval as from five to six weeks more than doubled their weight by virtue of the presence of the water-soluble vitamins supplied by the yeast, as compared with the failure of growth of littermate groups on the same diet and the same daily food and water intake that were denied the vitamin B complex.

TABLE 1.—*Summary of Results on the Influence of a Deficiency of the Vitamin B Complex on the Lipid Metabolism of the Albino Rat, Expressed as Milligrams per Hundred Cubic Centimeters of Blood*

	Avitaminotic Animals		Controls on Same Plane of Nutrition, but Which in Addition Received Vitamin B Complex	
	Range	Average	Range	Average
Cholesterol	81*–118†	93‡	72*–109†	75‡
Lecithin	361–610	473	319–515	406
Fatty acids	273–615	420	193–472	338
Iodine number (of fatty acids)	170–469	310	117–275	177

* Represents the average of all the minimum figures.
† Represents the average of all the maximum figures.
‡ Represents the average of all the determinations.

LIPID METABOLISM

Cholesterol.—While there was considerable fluctuation in this constituent during the experimental period in both the control and pathologic rats, the concentration of cholesterol was much higher in the avitaminotic animals, being least, by comparison with the controls, in group 1938-1939 and most in group 1966-1967 (chart 1). In group 1940-1941 the cholesteremia occurred during the last five weeks of the avitaminosis.

Lecithin and Fatty Acids.—It is quite apparent from charts 4, 5 and 6 that there is a higher concentration of both of these lipid constituents throughout the experimental period in the vitamin B-deficient animals.[12] It is also evident that, in the case of the fatty acids, the lipemia begins as early as from the first to the second week of vitamin B-depletion.[13]

Iodine Number.—The iodine number of the fatty acids represents the degree of unsaturation, and from the data submitted, we can con-

12. The term vitamin B is used here in the sense of the group of water-soluble vitamins referred to in this paper as the vitamin B complex.

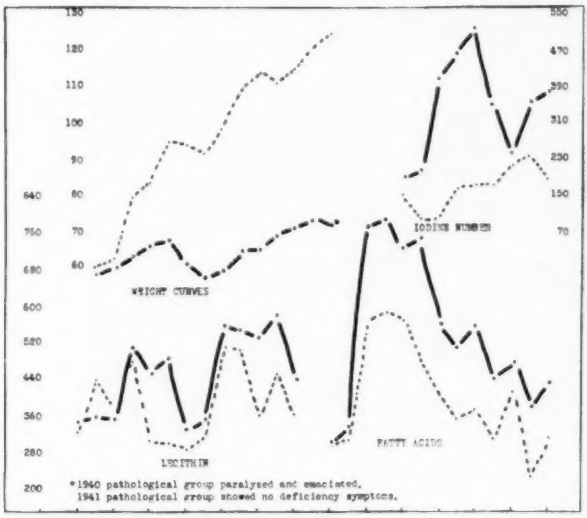

Chart 5.—Curves of weight, iodine number, lecithin and fatty acids for group 1940-1941. Each division on the horizontal scale indicates two weeks.

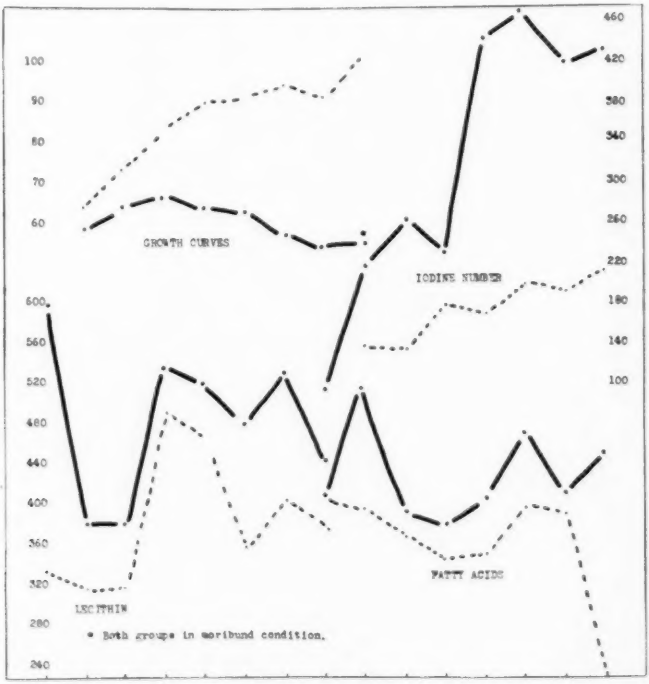

Chart 6.—Curves of growth, iodine number, lecithin and fatty acids for group 1964-1965. Each division on the horizontal scale indicates one week.

clude that a considerable proportion of the lipemia due to fatty acids belongs to the unsaturated series, since the iodine number of the blood of the avitaminotic animals was always higher than that of the controls.

In table 2 is presented a summary of the average figures for all the determinations throughout the period of experimentation, also the average minimum and maximum figures which constitute the range. An analysis of this table discloses the fact that in the disturbance of fat metabolism during vitamin B [12] deficiency the fatty acids show the greatest rise, the cholesterol the next greatest and the lecithins the least.

TABLE 2.—*Specific Effect of Deficiency of Vitamin B Complex on the Glycogen Content of the Liver*

Group	Animal	Age, Days	Sex	Weight, Gm.	Weight of Liver, Gm.	Weight of Dextrose per Liver, Mg.	Dextrose per 100 Gm. of Liver, Mg.	Dextrose, per Cent of Body Weight, Mg.
Pathologic	7515	65	♀	51	1.5876	7.91	498.24	15.51
Control	7516	66	♀	72	1.9735	13.78	698.25	19.14
Pathologic	7517	64	♂	51	1.7146	10.07	587.31	19.75
Control	7518	65	♂	68	2.1812	14.28	654.68	21.00
Pathologic	7519	116	♂	50	1.9664	8.01	407.34	16.02
Control	7520	117	♂	100	2.7828	11.33	407.14	11.33
Pathologic	7521	122	♀	94	2.5000	8.26	330.40	8.79
Control	7522	123	♀	147	4.1208	12.39	300.01	8.43
Pathologic	7631*	84	♂	54	2.0271	3.24	159.83	6.00
Control	7632	85	♂	102	3.4464	11.62	337.16	11.39
Pathologic	7633*	71	♀	43	1.6110	1.81	112.35	4.21
Control	7634	72	♀	79	2.7535	4.12	149.64	5.22
Pathologic	7635*	64	♀	36	1.5369	2.75	179.63	7.64
Control	7636	65	♀	97	3.3289	14.13	424.46	14.56
Pathologic	7637*	67	♂	55	2.7332	4.40	160.98	8.00
Control	7638	68	♂	92	3.3093	15.52	468.98	16.87

* Killed in moribund condition.

GLYCOGEN CONTENT OF THE LIVER

Our observations on the influence of vitamin B [12] deficiency on the glycogen content of the liver are summarized in table 2. The results are expressed in milligrams of dextrose per liver, per hundred grams of liver and per hundred grams of body weight. All the avitaminotic animals showed a considerable reduction in the glycogen, expressed as the amount of dextrose per liver. That the reduction in liver glycogen was not just proportional to the reduction of the weight of the liver is evident in that in 75 per cent of the cases the reduction of liver glycogen was much greater than the loss of liver weight. This is indicated by the figures showing the amount of dextrose per hundred grams of liver. The reduction of liver glycogen in the pathologic rats was also greater than the loss of body weight in 75 per cent of the cases. Since the plane of nutrition of the control animals that received the vitamin B complex

in the diet was restricted to that of the pathologic animals, the pronounced reduction in the glycogen content of the liver is attributable to the specific influence of this avitaminosis.

Since vitamin B deficiency is seldom found to exist in this country in an accentuated form as it occurs in the orient, manifested as a specific disease, beriberi, it is quite possible that for lack of cleancut clinical symptomatology, many borderline cases are missed. It is therefore suggested to the clinician that a chemical study of the blood lipids may be an aid to the prognosis of the need of vitamin B therapy, particularly in cases of malnutrition, associated not necessarily with a chronic anorexia, but with a lack of normal appetite. It is recognized, however, that cholesteremia is found in such diseases as diabetes and in chronic parenchymatous nephritis;[13] also that it may be present in other deficiency diseases. Therefore, it will be necessary to have the assurance that there is an adequate intake of vitamins A and D, which can be readily furnished by cod liver oil, and vitamin C, which can be supplied by orange and tomato juice, and that the patients are free from other diseases before a lipemia, if found, can be ascribed to vitamin B deficiency.

We are at present studying the lipid metabolism in other deficiency diseases.

SUMMARY

1. A deficiency of the vitamin B complex per se produces in the albino rat a lipemia, characterized by an increase in fatty acids, the iodine number of fatty acids, cholesterol and lecithins. The increase in concentration is in the order named.

2. A deficiency of the vitamin B complex per se produces in the albino rat a marked reduction in the glycogen content of liver.

3. It is suggested that the lipemia in the avitaminosis studied may have a clinical application.

13. Campbell, J. M. H.: Quart. J. Med. **18**:393, 1925.

AVITAMINOSIS

V. THE SPECIFIC EFFECT OF VITAMIN B DEFICIENCY ON THE DIFFERENTIAL COUNT OF THE ALBINO RAT *

BARNETT SURE, PH.D.
AND
DOROTHY J. WALKER, M.S.
FAYETTEVILLE, ARK.

In a recent communication Sure, Thatcher and Walker [1] have reported that in uncomplicated vitamin B deficiency there are produced a lymphopenia and a corresponding polymorphonuclear leukocytosis. The conclusion was, however, tentatively reached that such changes may be an expression of inanition. In this article we are submitting evidence showing that such a phenomenon is a manifestation of a deficiency of vitamin B per se.

Three groups of littermate rats of the same sex were studied in sets of four. The first animal received a diet satisfactory in every respect with the exception of vitamin B, 10 per cent autoclaved dehydrated yeast in the ration having supplied an adequacy of vitamin G. The second animal received the same diet and was restricted to the same amount of food and water daily as the first, but instead received the same proportion of untreated yeast in the ration, thus being supplied an abundance of vitamins B and G. The only limiting factor in the diet of the first animal was then vitamin B, and the difference in growth and the leukocyte picture of the blood between the first and second animals was then due to the specific influence of vitamin B, since the plane of nutrition was controlled. The third animal received the same diet and the same amount of food daily as the second animal, but was allowed water ad libitum. Consequently, any difference in physiologic and biologic findings between the second and third animal is attributable to the luxus consumption of water. The fourth animal was allowed the same diet as the second animal, but was unrestricted in its daily food and water intake. Therefore, the biochemical changes produced in the

* Submitted for publication, June 27, 1931.
* Research paper no. 237, Journal Series, University of Arkansas.
* From the Department of Agricultural Chemistry, University of Arkansas.

1. Sure, B.; Thatcher, H. S., and Walker, D. J.: Avitaminosis: I. Pathologic Changes in Nursing and in Weaned Albino Rats Suffering from Vitamin B Deficiency, Arch. Path. **11**:413 (March) 1931.

second animal as compared with the fourth are due to undernutrition or inanition.

In tables 1 to 4 we are giving typical results of one of these four group experiments.

TABLE 1.—*The Differential Leukocyte Count of Rat 7483 (Female) on a Diet Satisfactory in Every Respect with the Exception of Vitamin B*

Date	Age	Weight	Polymorphonuclears	Lymphocytes	Large Mononuclears	Eosinophils	Basophils
11/19/30	58	92	20	75	2	3	0
11/26/30	65	90	17	80	1	2	0
12/ 3/30	72	86	20	74	4	2	0
12/10/30	79	86	27	69	3	0	1
12/17/30	86	89	24	74	0	2	0
12/24/30	93	93	22	76	2	0	0
12/31/30	100	91	20	80	0	0	0
1/ 7/31	107	96	26	74	0	0	0
1/14/31	114	91	31	66	0	2	1
1/21/31	121	97	34	64	2	0	0
1/28/31	128	100	35	60	2	2	1
2/ 4/31	135	108	38	59	3	0	0
2/11/31	142	109	40	54	2	3	0
2/25/31	156	105	36	58	2	3	1
3/12/31	171	99	39	56	3	2	0
3/26/31	185	77	40	54	3	2	1
4/ 8/31	198	78	42	58	0	0	0
4/15/31	205	73	40	56	3	1	0

TABLE 2.—*The Differential Leukocyte Count of Rat 7484 (Female) on the Same Diet and the Same Food and Water Intake as Its Littermate, Rat 7483, but Which in Addition Received an Abundance of Vitamin B in Its Ration*

Date	Age	Weight	Polymorphonuclears	Lymphocytes	Large Mononuclears	Eosinophils	Basophils
11/19/30	58	89	18	80	1	0	1
11/26/30	65	87	27	73	0	0	0
12/ 3/30	72	88	28	65	2	4	1
12/10/30	79	85	33	62	3	2	0
12/17/30	86	93	30	66	2	2	0
12/24/30	93	98	23	64	0	2	1
12/31/30	100	94	21	78	1	0	0
1/ 7/31	107	108	18	80	0	2	0
1/14/31	114	110	20	77	2	0	1
1/21/31	121	110	21	75	2	1	1
1/28/31	128	115	24	71	2	2	1
2/ 4/31	135	115	20	75	2	3	0
2/11/31	142	124	21	75	2	2	0
2/25/31	156	135	23	75	2	0	0
3/12/31	171	127	24	73	2	1	0
3/26/31	185	125	22	76	0	2	0
4/ 8/31	198	115	20	77	0	2	1
4/15/31	205	114	17	80	2	0	1

The animals were bled peripherally, and the differential counts were made, the Wright stain being used. No differentiation was made between the small and large lymphocytes, all such cells having been grouped under lymphocytes.

In a previous publication, Sure, Kik and Walker demonstrated that there is no appreciable change in the total leukocyte count in this avitaminosis; therefore, the total count was deleted in this investigation.

It is apparent from the representative data submitted here that vitamin B per se produces an effect on growth; also that in this avitaminosis there results a lymphopenia to the extent of about 20 per cent with a corresponding polymorphonuclear leukocytosis, which is a direct

TABLE 3.—*The Differential Leukocyte Count of Rat 7485 (Female) on the Same Dietary Regimen as Its Littermate, Rat 7484; the Daily Food of This Animal Was Restricted to That Given Females 7483 and 7484, but Water Was Allowed ad Libitum*

Date	Age	Weight	Polymorphonuclears	Lymphocytes	Large Mononuclears	Eosinophils	Basophils
11/19/30	58	90	17	80	0	3	0
11/26/30	65	94	18	79	0	3	0
12/ 3/30	72	95	20	78	0	2	0
12/10/30	79	86	26	73	0	0	1
12/17/30	86	91	24	71	2	3	0
12/24/30	93	94	26	68	2	2	2
12/31/30	100	91	18	81	1	0	0
1/ 7/31	107	101	20	78	0	2	0
1/14/31	114	101	20	79	0	1	0
1/21/31	121	99	22	78	0	0	0
1/28/31	128	105	23	73	2	2	0
2/ 4/31	135	112	26	69	2	2	1
2/11/31	142	120	28	70	2	0	0
2/25/31	156	121	20	78	2	0	0
3/12/31	171	125	24	72	2	1	1
3/26/31	185	127	23	75	2	0	0
4/ 8/31	198	117	18	80	0	2	0
4/15/31	205	117	19	81	0	0	0

TABLE 4.—*The Differential Leukocyte Count of Rat 7486 (Female) on the Same Diet as Was Furnished Females 7484 and 7485; This Rat Was Unrestricted as to Its Daily Food and Water Intake; This Is the Positive Control*

Date	Age	Weight	Polymorphonuclears	Lymphocytes	Large Mononuclears	Eosinophils	Basophils
11/19/30	58	103	18	79	2	0	1
11/26/30	65	114	25	71	1	3	0
12/ 3/30	72	127	29	66	3	2	0
12/10/30	79	131	30	66	3	0	1
12/17/29	86	139	21	76	1	2	0
12/24/30	93	147	18	77	3	2	0
12/31/30	100	152	24	74	0	2	0
1/ 7/31	107	155	20	78	1	0	1
1/14/31	114	157	21	77	0	2	0
1/21/31	121	167	23	73	2	2	0
1/28/31	128	167	24	70	4	2	0
2/ 4/31	135	168	30	62	5	2	1
2/11/31	142	172	21	74	2	3	0
2/25/31	156	174	24	72	1	2	1
3/12/31	171	170	23	75	0	1	1
3/26/31	185	174	20	76	4	0	0
4/ 8/31	198	173	21	79	0	0	0
4/15/31	205	177	20	75	2	3	0

expression of vitamin B deficiency and not of inanition. The changes in the large mononuclears or monocytes and in the eosinophils and basophils are insignificant in this dietary deficiency. It is also evident that a liberal supply of water does not change the blood picture. The surprising fact in this study is that no apparent change was observed

in the differential count as a result of undernutrition. If a change were produced, rat 7486, whose intake was not restricted, should have shown different results from rat 7484, which was restricted to the same complete synthetic diet, but the lymphocyte-polymorphonuclear ratio was not disturbed throughout the whole experimental period.

In addition to the three groups of four, we have studied four sets of pairs according to the technic described in the first part of the paper. However, we were unable to substantiate these findings in four pairs of animals that were depleted of the vitamin B complex, i. e., on a diet deficient in both vitamins B and G, the reason probably being that the animals on such a dietary regimen succumbed before an opportunity was afforded for pathologic changes to be demonstrable in the blood stream.

SUMMARY

A deficiency of vitamin B per se produced in the weaned albino rat a lymphopenia to the extent of about 20 per cent, with a corresponding polymorphonuclear leukocytosis. No demonstrable changes were found in this avitaminosis in the monocytes, eosinophils or basophils.

EFFECT OF LIGATION OF THE PAROTID DUCTS ON THE CARBOHYDRATE TOLERANCE OF NORMAL DOGS *

LEO M. ZIMMERMAN, M.D.†
CHICAGO

During the period, about forty years ago, when Minkowski [1] was establishing a probable relationship between the pancreas and diabetes, two Italian workers, de Renzi and Reale,[2] reported diabetes in dogs following the extirpation of the salivary glands and of the duodenum. Minkowski felt that the removal of the duodenum could not be effected without at the same time materially damaging the pancreas. He repeated the experiments on the salivary glands and found a mild (from 1 to 3 per cent), inconstant, transient glycosuria after removal of these glands. He concluded that this glycosuria was nonspecific, that it was incidental to the operation or the anesthetic, and that the salivary glands had nothing to do with the control of the sugar metabolism. This is the view that, with very few exceptions, has prevailed regarding the function of the salivary glands.

In 1907, Ferrannini [3] reported a case of "salivary diabetes" in which the patient suffered from an excessive flow of saliva (several liters in twenty-four hours) that contained dextrose. Later it was found that glycosuria alternated with and replaced the glycosialorrhea. His interest being aroused in a possible reciprocal relationship between the salivary glands and the pancreas, Ferrannini entrusted to his assistant, Farroni,[4] a series of investigations concerning the function of the

* Submitted for publication, June 24, 1931.

* This work was aided by a grant from the Max Pam Fund for Metabolic Research.

* From the Metabolic Laboratory, Department of Physiology, Nelson Morris Institute for Medical Research, Michael Reese Hospital.

† Associate in Surgery, Northwestern University Medical School.

1. Minkowski: Weitere Mitteilungen ueber den Diabetes mellitus nach Exstirpation des Pankreas, Berl. klin. Wchnschr. **29**:90, 1892.

2. de Renzi and Reale: Ueber den Diabetes mellitus nach Exstirpation des Pankreas, Berl. klin. Wchnschr. **29**:560, 1892.

3. Ferrannini, A.: Glycosialorrhée de sécrétion interne des glandes salivaires, Rev. méd. de Paris **31**:269, 1911; Glycosialia and Glycosialorrhea, Riforma med. **44**:1249, 1928.

4. Farroni: Funzione endocrina delle glandole salivari ed eliminazione degli zuccheri, Rev. crit. di clin. med. **12**:577 and 593, 1911.

salivary glands. These studies showed that extracts of salivary glands of cattle exerted a glyco-inhibitory action in rabbits, preventing or controlling glycosuria following the administration of epinephrine, phlorhizine and morphine. In vitro, the extract exhibited marked glycolytic action (from 65 to 70 per cent) on different sugars. On the basis of these findings, Ferrannini postulated an endocrine action of the salivary glands analogous to that of the pancreas.

No significant confirmation of these findings appeared until 1924, when Goljanitzki [5] published results of experiments on the "substitution of endocrine glands." Among other things, he found that removal of both parotid and submaxillary glands in rabbits led to rapid emaciation and death, and glycosuria was noted. Ligation of the parotid duct prevented glycosuria due to epinephrine. In one patient with diabetic gangrene, ligation of the parotid duct was done, with strikingly beneficial results. In a later publication additional cases were described in which ligation of the parotid ducts and transplantation of the submaxillary gland seemed to influence favorably the symptoms of diabetes.

Mansfeld,[6] of Budapest, in 1928, sought a surgical cure for diabetes. He found that ligation of part of the pancreas increased the production of insulin. He reasoned that obstruction to the external secretion resulted in increased internal secretion. On the basis of this and of the fact that glands of internal secretion ontogenetically and phylogenetically are external secretory glands which develop an endocrine function when they lose their excretory ducts, he assumed that any gland of external secretion could be converted into one of internal secretion by depriving it of its excretory duct. Because the salivary glands resemble the pancreas embryologically and morphologically, and because both are concerned with digestion of carbohydrates, he anticipated that ligation of their ducts would convert them into endocrine glands with an insulin-like secretion. He accordingly ligated the parotid ducts of two dogs, and found that the blood sugar levels, particularly the starvation levels, were lowered. Later, the ligated glands were extirpated, and the sugar levels returned to their preoperative values. Two additional dogs were depancreatized, and the parotid ducts were then ligated, with resulting control of the diabetes. Total extirpation

5. Goljanitzki, J. A.: Zur Frage des Ersatzes der endokrinen Druesen, Arch. f. klin. Chir. **130**:763, 1924; Zur Frage der inneren Sekretion der Speicheldruesen und ihre klinische Bedeutung, Deutsche Ztschr. f. Chir. **191**:79, 1925. Goljanitzki and Smirnowa: Weitere Erfahrungen mit der chirurgischen Behandlung des Diabetes, Ztschr. f. klin. Med. **105**:661, 1927.

6. Mansfeld, G., and Szirtes, L.: Ueber die Beziehungen zwischen aeusserer und innerer Sekretion der Druesen, Arch. f. exper. Path. u. Pharmakol. **130**:1 and 28, 1928. Mansfeld, G.: Versuche zu einer operativen Behandlung des Diabetes, Klin. Wchnschr. **7**:14, 1928. Mansfeld, G., and Schmidt, E.: Versuche zu einer operativen Behandlung des Diabetes, Klin. Wchnschr. **7**:1457, 1928.

of the pancreas in an animal in which the parotid ducts were ligated, however, produced just as severe diabetes as in normal animals. It was thought, therefore, that the action was an indirect one, a substance being produced in the parotid glands that stimulated the pancreas to increased function. Two patients were operated on, but the results were not stated. Seelig,[7] of Berlin, repeated these experiments and confirmed Mansfeld's findings. He subsequently reported a series of eighteen cases of diabetes in which ligation of the parotid ducts was done, with definite amelioration of symptoms in some of the cases. The number of cases was too small and the period of observation too short to permit the drawing of definite conclusions. De Takáts[8] confirmed Mansfeld's findings following ligation of the tail of the pancreas, and recently reported two cases of juvenile diabetes in which the clinical course of the disease was favorably influenced by this operation.

The results reported following ligation of the parotid ducts seemed to my co-workers and me to be of sufficient significance to warrant further investigation. Accordingly, determinations of sugar tolerance were made in a series of dogs before and after ligation of both parotid ducts. Healthy, normal animals were selected for this work, of sufficient size to permit repeated venipunctures for the injection of sugar solutions and for the collection of blood samples. The animals were kept on a known controlled diet, consisting of lean meat and milk. They were fed once daily, at the same hour. In the earlier experiments, the sugar for the dextrose tolerance tests was administered by mouth. Later, to obviate irregularities in the rate of absorption, all dextrose solutions were injected intravenously at a timed rate. Blood samples were taken immediately before the injection of dextrose, and at intervals of fifteen, thirty, forty-five, sixty and one hundred and twenty minutes thereafter. The determinations of the blood sugar were done by the modified Folin-Wu method, in the chemical laboratory of the Nelson Morris Institute for Medical Research.

It was found that repeated determinations of dextrose tolerance, by the method described, gave results that usually checked very closely. We are aware that this is in variance with the experience of others. We feel that if conditions are maintained as nearly uniform as possible, most dogs will give blood sugar curves that coincide very closely.

---

7. Seelig, S.: Ueber Beziehungen zwischen Parotis, Pankreas, Blutzucker und Diabetes mellitus, Klin. Wchnschr. **7**:1228, 1928; Zur chirurgischen Behandlung der Zuckerkrankheit, Arch. f. klin. Chir. **157**:322, 1929.

8. de Takáts, G.: Ligation of Tail of Pancreas in Juvenile Diabetes, Endocrinology **14**:255 (July-Aug.) 1930. de Takáts, G.; Hannett, F.; Henderson, D., and Seitz, I. J.: Correlations of Internal and External Pancreatic Secretion: IV. Effect of Isolation of Tail of Pancreas on Carbohydrate Metabolism, Arch. Surg. **20**:866 (May) 1930.

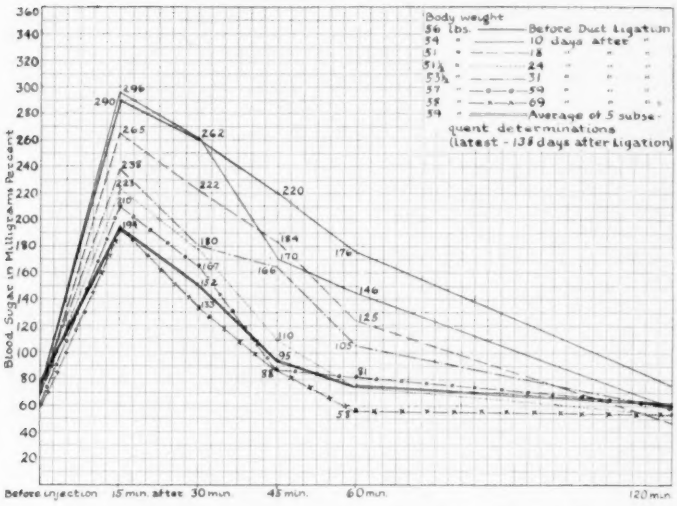
Body weight
56 lbs. Before Duct Ligation
54 " 10 days after "
51 " 18 " " "
51½ " 24 " " "
53½ " 31 " " "
57 " 59 " " "
58 " 69 " " "
59 " Average of 5 subsequent determinations (latest - 138 days after ligation)
Blood Sugar in Milligrams Percent
Before injection
15 min. after
30 min.
45 min.
60 min.
120 min.

Fig. 1 (dog 38).—Curves showing sugar tolerance before and at intervals after ligation of the parotid duct.

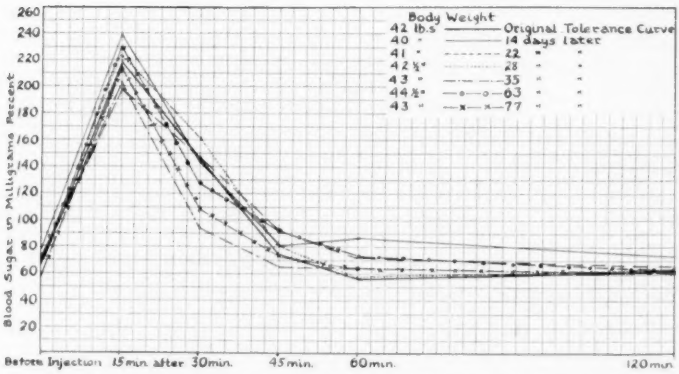

Fig. 2 (dog 39).—Control for chart in figure 1. Determination of sugar tolerance in an animal that was not operated on, made in the same manner and at intervals corresponding to those in the preceding chart.

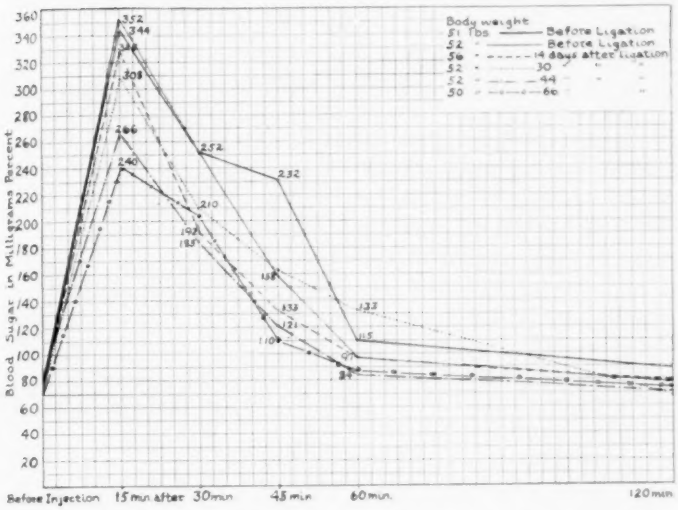

Fig. 3 (dog 40).—Effect of ligation of the parotid duct on dextrose tolerance curves.

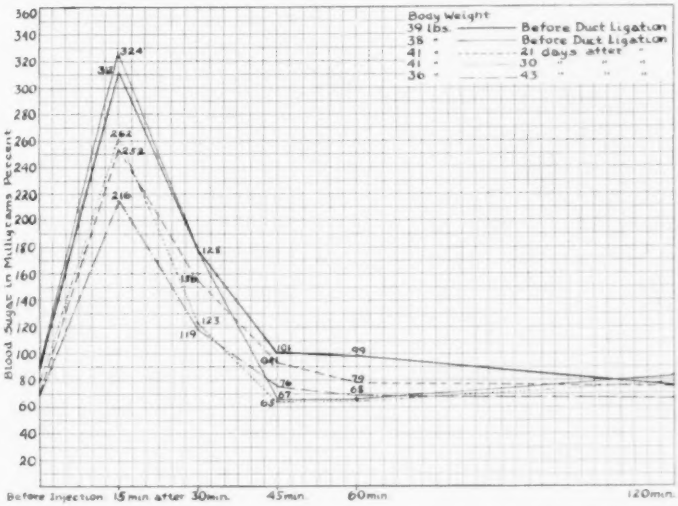

Fig. 4 (dog 43).—Tolerance curves, showing dextrose tolerance before and after ligation of the parotid duct.

Occasionally an animal is encountered for which it is difficult to attain the usual type of curve and such animals should not be used for these experiments. In our experiments, the dogs were kept on the controlled diet for several weeks before the determinations were begun. They were fed and handled by the same keeper, and his familiarity with them overcame much of the apprehension and excitement of the subsequent determinations. Repeated determinations were made on each animal at the beginning of the experiment. The concentration of the dextrose solution and the time of injection were kept as constant as was possible.

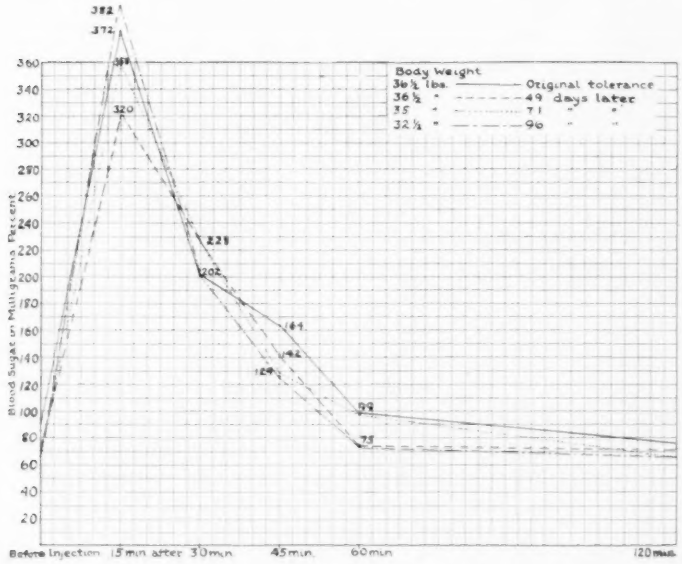

Fig. 5 (dog 44).—Control for charts in figures 3 and 4. No similar fall in blood sugar curves is seen in an animal that was not operated on.

The determinations of blood sugar were made by persons entirely unfamiliar with the identity of the animals from which the specimens were taken. Duplicate determinations were made at sufficiently frequent intervals to insure the accuracy of the methods. Two groups of control animals were used, one in which the tolerance studies were repeated at about the same intervals as in the experimental animals and another in which a sham operation was done that involved approximately the same amount of dissection in the same region as in the experimental animals, but in which the parotid ducts were not disturbed.

All surgical operations were done under ether anesthesia, with morphine premedication and with the usual aseptic precautions. Before

the parotid ducts were ligated, the two cheeks were shaved and prepared with tincture of iodine. An incision about three-fourths inch (2 cm.) long was made in the line joining the angle of the mouth with the posterior margin of the cartilage of the ear, over the prominent portion of the masseter muscle in the cheek. The masseter muscle was

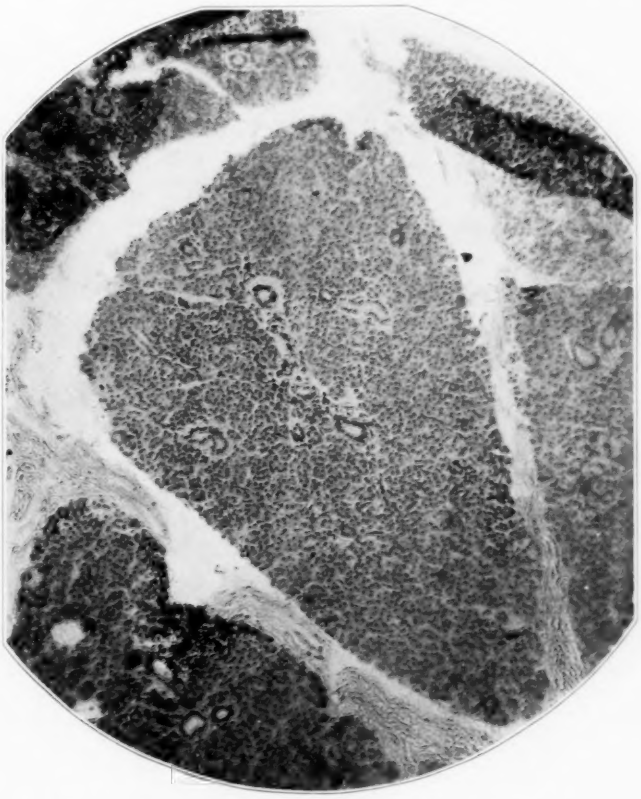

Fig. 6.—Photomicrograph of normal dog's parotid gland.

exposed, and the duct was readily seen as a fine, translucent, straight structure, lying just beneath the fascia over the muscle, and running in the direction of the muscle fibers. The only structures that might be mistaken for the duct are the branches of the facial nerve. These, however, lie slightly more superficially, are more opaque and less direct in their course and, if followed, are seen to branch or to unite with adjacent branches. The ducts were doubly clamped and ligated with silk,

and the intervening segments, usually about 1 cm. long, were excised. If any doubt existed as to the identity of the duct, the segment that had been removed was sectioned. The fascia over the ligated duct was closed with a few interrupted, fine catgut sutures, and the skin was united with an intradermal stitch. As a rule, no dressing was applied.

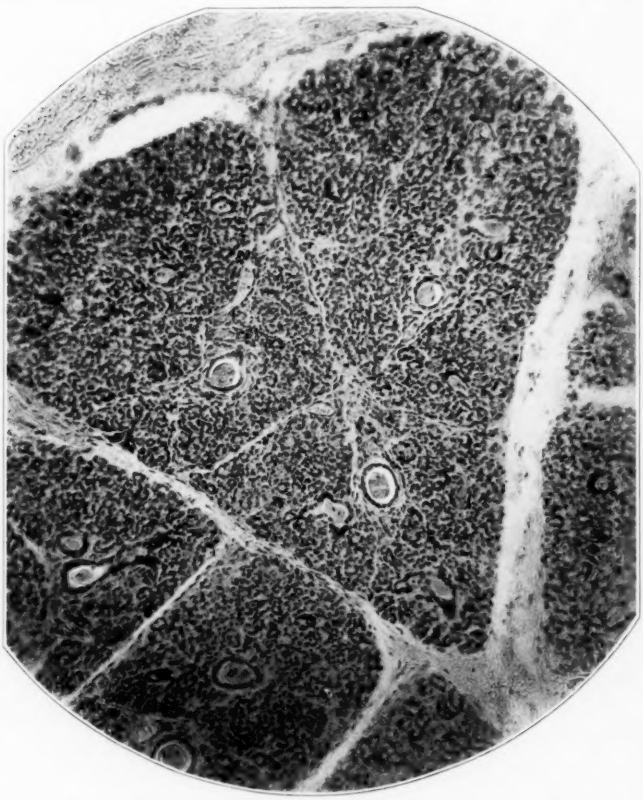

Fig. 7.—Section of parotid gland thirteen days after ligation of the duct. Note dilatation of secretory ducts.

The animals withstood the operation very well. Marked swelling of the parotid gland was apparent at the end of twenty-four hours; it reached its maximum in from two to three days, and then gradually subsided. In some of the animals the wounds opened, discharging serous secretion. In none were there persisting salivary fistulas. Postoperative determinations of the sugar tolerance were not made until the wounds had entirely healed and the animal seemed to have entirely recovered

from the operation. During fasting there was no constant change in the blood sugar levels of our animals as a result of the ligation of the parotid ducts. There was, however, a definite increase in the sugar tolerance, as measured by a lower blood sugar curve and by a rapid return to normal levels following the injection of dextrose solutions.

Fig. 8.—Parotid gland fifty-eight days after ligation of the duct. The secretory ducts are dilated and there are atrophy and fibrosis of the parenchyma.

This is well demonstrated in the charts. The first postoperative determination of sugar tolerance usually showed a curve higher than those before operation. This is to be attributed to the disturbance in metabolism caused by the operation and the anesthetic. Subsequent curves showed a progressive lowering of tolerance, reaching the lowest levels from four to five months after the operation and then remaining con-

stant. There were no decided changes in the body weight or in the general condition of the animals.

In some of the animals, the ligated glands were subsequently removed in order to determine what effect that would have on the carbohydrate tolerance. These experiments were not conclusive. In most of the animals, however, there was some increase in the height of the blood

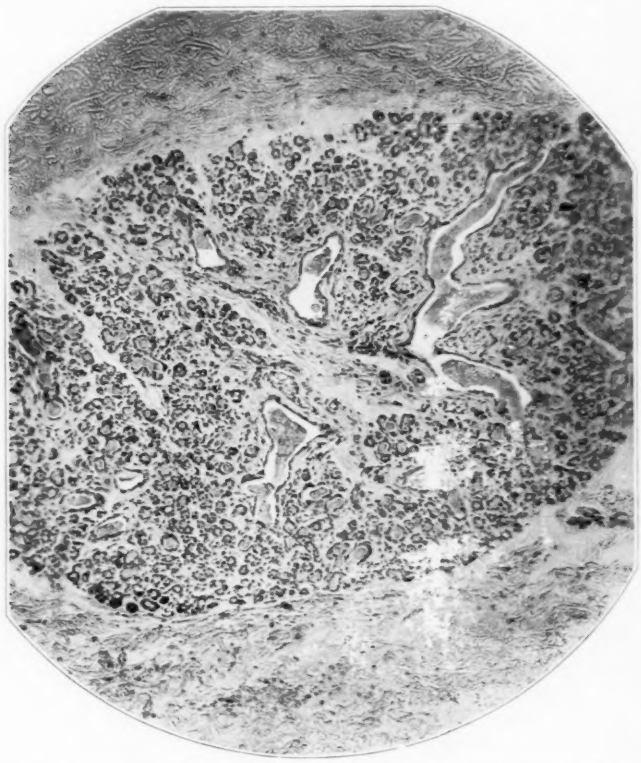

Fig. 9.—Parotid gland one hundred and thirteen days after ligation of its duct. The secretory ducts are greatly distended and there are marked atrophy and cirrhosis of the gland.

sugar curve after the removal of the glands. The extirpation of the parotid glands could not always be satisfactorily performed. These glands in the dog are not sharply circumscribed, but are spread out, being widely distributed in the deep fascia of the face. To insure removal of all glandular tissue, it is necessary to make a block dissection of the deep fascia down to the muscles, extending from the zygomatic

ridge above to the masseter muscle anteriorly, the ear posteriorly and the submaxillary gland below. So extensive a dissection requires the sacrifice of nerves and blood vessels, and is attended with considerable postoperative swelling and not infrequently with delayed healing of the wound. Even then one cannot be sure that all traces of glandular tissue have been removed.

Parotid glands were removed at varying intervals after the ligation of their excretory ducts, and the specimens were examined microscopically. Prof. R. R. Bensley, of the department of anatomy of the University of Chicago, studied these preparations. He reported a very slow but gradual dilatation of the salivary ducts, with atrophy and fibrosis of the gland parenchyma. Nowhere did he find evidence of proliferation of the gland or of the development of abnormal types of cells.

COMMENT

The results of these experiments indicate that the parotid glands of the dog exert some influence as yet not recognized on the control of the carbohydrate metabolism. This is of some significance in view of the total ignorance as to the purpose of the salivary glands. As Professor Bensley expressed it, aside from secreting some slipperiness and wetness, they have no known function. Even the well known digestive function is absent in certain species of animals. It has frequently been suggested that perhaps these glands might have an internal secretory action as well as their external secretory one. The frequent association of orchitis and oophoritis with inflammation of the parotid glands in epidemic parotitis has suggested a relationship between the salivary glands and the gonads. The resemblance between the parotids and the pancreas has already been pointed out. Both structures have their origins as ventral out-pouchings from the primary intestine. Both are concerned with the elaboration of digestive enzymes, specifically those of a starch-splitting nature. Pancreatitis occurring during or after epidemic parotitis has been described (Farnam,[9] Stevens[10]), and fatal cases of diabetes have followed mumps (Patrick,[11] Gundersen[12]); conversely, hypertrophy and inflammation of the parotid glands have been noted in diabetic patients.

The results of our experiments confirm the findings of Goljanitzki,[5] Mansfeld[6] and Seelig.[7] They indicate a relationship between the sali-

9. Farnam, L. W.: Pancreatitis Following Mumps, Am. J. M. Sc. **163**:859, 1922.

10. Stevens, A. M.: Mumps of the Pancreas, Arch. Pediat. **42**:333, 1925.

11. Patrick, A.: Acute Diabetes Following Mumps, Brit. M. J. **2**:802, 1924.

12. Gundersen, E.: Is Diabetes of Infectious Origin? J. Infect. Dis. **41**:197 (Sept.) 1927.

vary glands and the carbohydrate metabolism. The nature of the action is as yet unknown. In a few experiments by Mansfeld, ligation of the parotid ducts was found to be without effect in totally depancreatized animals. These results have been confirmed by Dr. Samuel Saskin and me.[13] This would indicate that the action is not a primary insulin-like one, but rather that it stimulates or activates the pancreas to secretion of insulin. Such an action might well be hypothecated. Just as the saliva stimulates the gastric glands to secrete gastric juice in anticipation of its need, so the salivary glands may stimulate the pancreas to elaborate insulin in anticipation of an increased need consequent on the taking of food. The persistence of the effect after the ligated glands have been removed suggests that possibly an antisubstance has been prevented from reaching the alimentary tract by the ligation of the duct and thus has increased the tolerance. The absence of any proliferative changes in the excised glands and the fact that progressive cirrhosis was the only finding are the strongest arguments against the existence of any positive secretion. Further work is in progress in an attempt to determine some of these facts.

CONCLUSIONS

1. Ligation of the parotid ducts in normal dogs results in an increased dextrose tolerance, as measured by the height of the blood sugar curve following the injection of dextrose solution.

2. Histologic study of parotid glands removed at varying intervals after ligation of their ducts reveals only gradual dilatation of the ducts, with atrophy and fibrosis of the glandular parenchyma.

3. Extirpation of the parotid glands in which the ducts had been ligated produced inconstant effects on the carbohydrate tolerance. Usually there was some increase in the height of the blood sugar curve, but the values rarely returned to the levels that had been maintained before the ducts were ligated.

4. Further work is in progress to determine the source and nature of the relationship between the parotid glands and the carbohydrate metabolism.

---

13. Zimmerman, Leo; and Saskin, Samuel: Effect of Ligation of the Parotid Duct on the Carbohydrate Tolerance of Totally Depancreatized Dogs, Arch. Int. Med., to be published.

CHOLESTEROL-THORAX IN TUBERCULOSIS (CHOLESTEROL PLEURISY)

REPORT OF A CASE *

HARRY M. STEIN, M.D.
BALTIMORE

The accumulation of fluid in the pleural cavities is a common condition, a number of interesting types having been encountered, and in all probability the rarest of these is that known as cholesterol pleurisy or sometimes spoken of as cholesterol-thorax. Cholesterol is constantly found in the tissues and is also rather uniformly found in all pleural effusions, but in the latter it is practically always present as an ethereal salt. The majority of writers on this subject agree that the condition should be defined as an effusion that is rich in cholesterol in crystalline form, and further, that the total amount of cholesterol in the effusion may be high or low, the amount not always determining the form in which it is found. In some cases reported the total amount of cholesterol has been high and in others there has been much less, but in all instances one should be able to demonstrate the crystals in great numbers. Thus the microscopic examination of the pleural fluid exhibits the very typical and characteristic crystals which are peculiar to crystalline cholesterol. Textbooks and authorities on diseases of the chest give the condition scant mention and on inquiring among my colleagues I can find no instances in their experiences in which cholesterol pleurisy has been observed. In a search of the literature twenty-one cases have been discovered, and the great majority of these are found in foreign journals, the condition apparently having been given much more attention in other countries than in our own. The first case was said to be reported by Guenau de Mussy, and in 1882 Churton [1] called attention to two cases, one occurring in a man of 38 years who had a bilateral hemorrhagic pleural effusion containing much cholesterol and who subsequently developed an empyema and supposed septicemia. This patient had a history suggestive of a tuberculous infection at the age of 18 years, and at autopsy several suggestive areas were demonstrated in the apex of the left lung, but unfortunately no microscopic studies of this tissue are reported. Another case occurred in a man of 31 years who had a previous pleural effusion and who ultimately died of

* Submitted for publication, June 1, 1931.

* Read before the American Climatological and Clinical Association, Hot Springs, Va., May 8, 1931.

1. Churton, Thomas: Tr. Clin. Soc., London **15**:9, 1882.

cirrhosis of the liver, the autopsy showing no tuberculosis. In 1907 Hedestrum published the report of a case of this condition, and in 1908 Ruppert [2] and Hess reported cases. Caussade described a case in 1914 in a man of 27 years who had previously had a pleural effusion that was probably tuberculous. In 1917 Schulman [3] observed a man of 62 years who had also had a previous pleural effusion, and in the same year Arnell [4] reported on this condition. In 1918 Weems [5] reported the case of a patient who had had a previous pleural effusion, and it was his opinion that the condition of cholesterol pleurisy was probably associated with faulty cholesterol metabolism, his patient having a definite increase in blood cholesterol.

In 1919 Izar [6] and Sharpe [7] published instances of cholesterol pleurisy, the latter citing two cases, one of which was definitely associated with tuberculosis. The other case occurred in a boy of 9 years who probably had a pleural tuberculosis.

Other cases were reported in 1924 by Stockman [8] and Coyon,[9] the patients in the latter's two cases both having tuberculosis. Mainini [10] described two cases in 1925, both patients having tuberculosis. Rouillard and Nativelle,[11] in 1927, told of a case occurring in a woman who had had a pleural effusion twenty-one years previously.

In making an effort to analyze these reports, one is immediately impressed with the frequency with which tuberculous infection is encountered in patients having cholesterol-thorax. In a considerable number of instances these patients have definite pulmonary tuberculosis, and in the majority of cases a history of previous pleural effusion is noted which was apparently primary in origin, and in the light of present-day thinking would be looked on as being probably tuberculous. It is striking also to note that these effusions occurred frequently many years before the patient was seen with cholesterol-thorax. With the exception of one case in a child of 9 years, reported by Sharpe, all of the other patients were adults and many of them beyond the fourth decade of life. Only a very few of the patients were women. It goes without saying that apparently the condition follows a chronic

2. Ruppert: München. med. Wchnschr. **55**:510, 1908.
3. Schulman, M.: Pleural Effusion, J. A. M. A. **68**:1256 (April 28) 1917.
4. Arnell, P.: Hygiea **79**:737, 1917.
5. Weems, B. F.: Am. J. M. Sc. **156**:20, 1918.
6. Izar: Riforma med. **35**:961, 1919.
7. Sharpe, H.: Brit. M. J. **2**:462 (Oct. 11) 1919.
8. Stockman, J.: Paris Thèses, 1924.
9. Coyon, A.; Fiessinger, N., and Meignant, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **48**:943 (June) 1924.
10. Mainini, C.: Bull. et mém. Soc. méd. d. hôp. de Paris **49**:1534 (Dec.) 1925.
11. Rouillard, J., and Nativelle: Bull. et mém. Soc. méd. d. hôp. de Paris **51**: 1717 (Jan.) 1927.

pleural inflammation, the type of the preceding inflammatory fluid being invariably serofibrinous or hemorrhagic.

Clinically, the disease must be looked on as chronic, usually not fatal in itself, and manifested by cough, dyspnea, very little if any expectoration and practically no constitutional symptoms such as fever, rapid pulse and toxemia. When postmortem material could be studied, the changes were invariably those of a long-standing chronic condition with much thickening of the pleurae, and in some instances calcification had ensued. When chemical determinations of the blood have been made, there seems to be no constancy as to the cholesterol values noted in the blood of these patients. Not many instances of complications were encountered, although rupture of the fluid into a bronchus might occur, and in some of the cases observed the fluid became purulent, but the question of frequent punctures in order to relieve pressure might have entered into this in the way of secondary infection. The diagnosis of the condition is made entirely by aspiration of the chest on the basis of physical findings, indicating the presence of fluid in one or both pleural cavities. When aspirated, this fluid might be found to be brownish, sometimes yellow or dirty white, and it is usually thin. It has a satin-like appearance, and grossly one can note the presence of a sheeny material in suspension. The specific gravity of the fluid has a wide range. It usually does not contain organisms, and microscopic examination shows myriads of cholesterol crystals in their very typical form. In none of the reports is any mention made as to the demonstration of tubercle bacilli in this fluid.

As for treatment, it seems that some cases would probably not need any, but the symptoms are usually those of respiratory embarrassment, and frequent aspirations of the fluid would be the correct procedure. Surgical measures should not be considered unless invasion of the fluid with micro-organisms occur.

The following case is cited from the private medical service at the University Hospital, Baltimore.

REPORT OF A CASE

History.—This history was obtained from relatives and in part from the patient. G. A., a man, white, complained of headache, dizziness, vomiting and fever of ten days' duration. The family history was not significant. For many years the patient had been prone to take "cold" easily, and about two weeks before admission to the hospital, just before the beginning of the present illness, he had an attack of "grip." At the age of 20 years he had an illness which was said to be pneumonia, and since that time he had had cough and bronchitis every winter, the cough being most noticeable in the morning and accompanied by a yellowish sputum. After his attack of pneumonia, he stated that the doctor aspirated some fluid from the left side of his chest on one occasion, but he did not remember any further details although he was sick at that time for a number of weeks. Seven

years before the present illness he had an attack of severe pain in the region of the left kidney, which occurred off and on for several weeks, but there was no definite diagnosis made as to the condition then. There was no history of venereal disease. The patient's habits were not unusual.

The patient was admitted to the University Hospital on Jan. 22, 1930, complaining of headache, vomiting and some "gas on the stomach" for the past ten days. His wife stated that he had been irrational for the past forty-eight hours. His headaches had been persistent, his temperature has ranged from normal to 101.5 F., and he had had several chills.

According to the pulmonary history, there had been rather constant shortness of breath on exertion. Fifteen pounds (6.8 Kg.) in weight had been lost in the last year. The gastro-intestinal history was not important. The cardiovascular renal history, genito-urinary history and history of the special senses showed a normal condition.

Physical Examination.—Jan. 23, 1930: Physical examination showed a white man, aged 45, who resisted examination and was disoriented; he looked quite ill, and there was evidence of undernutrition.

The head was entirely normal except for slight redness of the throat.

Except for slight rigidity, the neck was normal.

Examination of the heart and blood pressure showed nothing unusual. The lungs were normal except that on the left side the percussion note was impaired in the entire axillary space from the apex to the base and from the fourth rib in front down to the base, impairment blending with cardiac dulness. Posteriorly, the percussion note was impaired from the angle of the scapula to the base and was perfectly flat. The breath sounds over the left part of the back, except at the extreme apex, were absent. The base of the right lung descended well on deep inspiration.

The spine and abdomen were normal.

The reflexes of the extremities were all present and normal. There was no evidence of paralysis.

Otherwise, the results of the physical exaination were negative.

Laboratory Reports.—The urine was normal except for the fact that on several occasions a trace of albumin was noted.

The blood was normal morphologically. Cultures were negative. Chemical examination showed 74 mg. of cholesterol (whole blood) per hundred cubic centimeters. The Wassermann reaction was negative.

On January 22, the spinal fluid came out under a slight increase of pressure, increased by compression of the jugular vein; it was cloudy, contained 4 plus globulin and 348 cells per cubic millimeter. Practically all the cells were lymphocytes. The colloidal gold curve was 0134344321.

On January 24, the spinal fluid was unchanged except for an increase of cloudiness and the finding of 820 cells per cubic millimeter. In neither one of the two specimens of spinal fluid were organisms of any sort demonstrated. The predominant cell was a lymphocyte. Cultures made from the spinal fluid were entirely negative, and cultures made on special potato mediums did not grow tubercle bacilli. There was 23 mg. of spinal fluid sugar per hundred cubic centimeters.

Exploratory Thoracentesis.—January 23: Exploratory puncture was made in the seventh intercostal space on the left side posteriorly, and considerable resistance was met with in the entrance of the needle through the pleura, giving one the feeling of a very hard, thick pleura. A dirty white, milky fluid was obtained. It did not have any odor and when shaken in a test tube looked very much like thin

milk. The fluid showed no pus cells or organisms and contained no fat. Myriads of typical cholesterol crystals occupied the entire microscopic field.

The specific gravity was 1.024; water, 80 per cent.

The cholesterol content was 2,353 mg. per hundred cubic centimeters of the fluid.

No organisms could be demonstrated by direct smear. Tubercle bacilli were especially sought but none found. Later, all cultures made from the fluid proved to be negative.

Fig. 1.—Roentgenogram of the chest. The abnormal shadows on the left side are due to calcification of the pleura and fluid.

Pathologist's Report on Guinea-Pigs' Inoculation: January 29: Pigs were inoculated with a specimen of the spinal fluid.

March 20: Postmortem examination of the pigs showed disseminated tuberculosis.

Radiologic Examination (by Dr. H. J. Walton).—January 24: Roentgen examination of the chest showed a very dense, partially calcified shadow in the axillary region and base of the left lung. The shadow appeared to lie close to the chest wall and surrounded the lung. The mass obscured the detail of the lung. The upper portion of the lung above and to the mesial side of this shadow was clear and well aerated. The entire right lung was clear. There was also a slight calcification in the axillary region of the right base about 1 inch above the diaphragm.

The heart was of medium size, and was slightly displaced to the right side. The aorta was normal in width.

The impression was that there was extensive calcification of the pleura surrounding the lower axillary areas of the left lung and beginning calcification of the pleura in the axillary region of the base of the right lung.

The gastro-intestinal tract was normal.

Final Note.—January 30: It is believed from the history that the patient had some type of pleural effusion at the age of 20 years that had become cholesterol-

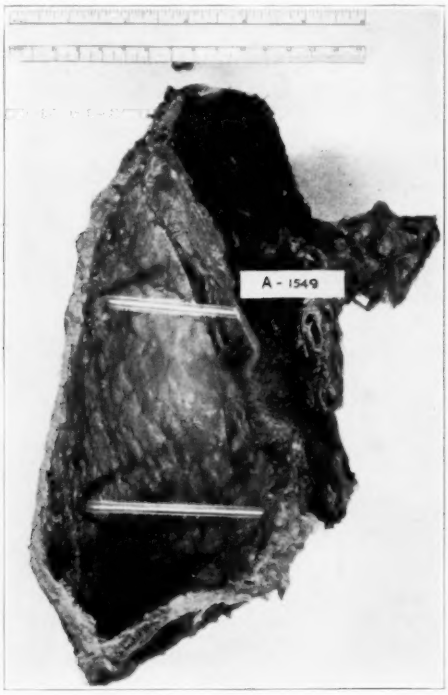

Fig. 2.—Lung specimen showing thickened calcified pleura and large cavity (held open by glass rods) which contained cholesterol.

ized. One might assume that he possibly had a pleural effusion long ago that was tuberculous in origin, and it is most interesting to note that the cause of the patient's death was tuberculous meningitis. It has been noted before that tuberculosis is an invariable finding in cases of cholesterol-thorax.

The final diagnosis was tuberculous meningitis and cholesterol-thorax.

Abstract.—Autopsy was performed by Dr. W. C. Merkel, of the department of pathology, University of Maryland.

The body was that of a well developed, though somewhat emaciated, white man. The external examination gave negative results. The peritoneum and abdominal organs as examined in situ appeared normal.

On removing the sternum, it was found that both pleural cavities were obliterated. On the right side, the lung was bound to the chest wall by dense fibrous adhesions. The right lung was voluminous, heavy and purplish red. Throughout this lung there were small granular areas of consolidation.

The left pleural sac presented an unusual picture. The left lung was much compressed and pushed upward and toward the midline. The parietal pleura at the base and about the sides of the pleural cavity and the visceral pleura over the anterior, lateral and posterior surfaces of the lung were thick and rigid. By careful dissection, the lung and thickened pleural sac were removed en masse. A study of the specimen showed the lung compressed about the large bronchi. On the surface of the lung there was attached a boxlike mass which assumed the shape of the cavity from which it had been removed.

This mass was extremely hard; it measured 23 cm. from apex to base, 24 cm. across its convex anterolateral surface at its widest portion and about 14 cm. in its greatest anteroposterior dimension. The wall was hard and gritty; it was cut through with the aid of a bone saw. On section, it was found that this mass was a closed cavity containing about 1,400 cc. of a milky fluid in which shimmering particles were seen. The wall was irregular, varying from 6 mm. to 2 cm. in thickness; it was composed of hyalinized fibrous tissue and contained masses of calcareous material and spicules of bone. In the thickened visceral pleura near the apex of the lung, there was a fibrocaseous nodule which measured about 1 cm. in diameter.

The brain showed a moderate injection of the vessels of the pia-arachnoid with some slight thickening of the leptomeninges. Typical tubercles embedded in a tuberculous granulation tissue involved the leptomeninges. No tubercles were found in the brain tissue.

A study of the other organs revealed little of interest. There was no evidence of tuberculosis except in the pleura and in the meninges.

Anatomic Diagnosis.—The anatomic diagnosis was: fibrocaseous tubercle of the visceral pleura, near the apex of the left lung; tuberculous meningitis; fibrosis, calcification and ossification of visceral and parietal pleura of the left lung; "cholesterol-thorax" of the left lung; partial atelectasis of the left lung; acute bronchopneumonia of the right lung; old pleural adhesions of the right lung, and moderate generalized arteriosclerosis.

COMMENT

1. The case report is that of cholesterol pleurisy occurring in a man who had a previous history of pleural effusion following pneumonia. I venture the opinion that in the absence of a clearer history it might be that the condition was originally one of tuberculous pleurisy with effusion and not of pneumonia. It is interesting to note that this patient actually did have tuberculosis involving the central nervous system many years after his probably tuberculous pleurisy, and that there was also autopsy evidence of a tuberculosis of the pleurae.

2. Cholesterol-thorax might be looked on in the majority of instances as an unusual end-result of a long-standing pleural effusion which was originally tuberculous in origin. One might assume that in view of the fact that the majority of primary pleural effusions are tuberculous in origin the condition of cholesterol-thorax simply means that an

old tuberculous effusion that has not been cured and has not caused death will in some instances eventually become cholesterolized.

3. The question of cholesterol metabolism is, of course, as yet an unsolved problem, and it may be possible that the only cases in which an old pleurisy becomes cholesterolized is in persons who have an abnormal cholesterol chemistry, this observation, of course, being theoretical.

In pulmonary tuberculosis, the reports vary as to the cholesterol chemistry, and it would seem that the cholesterol content in the blood in tuberculous infections may be increased or decreased. Eichelberger and McCluskey [12] claim that a rising or stationary hypercholesterolemia indicates immunity and resistance, while a falling blood cholesterol or a low blood cholesterol indicates a lowering in the immunity and resistance.

12. Eichelberger, L., and McCluskey, K. L.: Chemical Studies in Tuberculosis: I. Plasma Proteins, Cholesterol and Corpuscle Volume, Arch. Int. Med. **40**:831 (Dec.) 1927.

CARCINOMA OF THE GASTROJEJUNAL STOMA FOLLOWING OPERATION FOR PEPTIC ULCER *

HARRY A. SINGER, M.D.
CHICAGO

Since gastro-enterostomy came into general use in the treatment for peptic ulcer and its complications, certain nosologic entities previously practically unknown have loomed into prominence. Gastrojejunal ulcer, a unique and unimportant lesion prior to the era of gastro-enterostomy, is now accorded a great deal of space in treatises on peptic ulcer. High intestinal obstruction accompanied by symptoms of a vicious cycle evoked little attention until the universal adoption of gastro-enterostomy, after which an enormous literature appeared on the subject. To these more common sequelae of the anastomosis can be added carcinoma of the stoma, an extremely rare but interesting condition.

The occurrence of a malignant growth at the site of a gastrojejunal anastomosis was mentioned by Schwarz [1] in a paper dealing with observations at operation in gastro-enterostomized persons. The author gave an account of a patient who had an anterior gastro-enterostomy performed in 1909 for pyloric ulcer. The patient felt well for about six years, after which he began to lose weight and to vomit. Laparotomy disclosed a huge dilatation of the proximal loop and collapse of the distal loop. The cause of obstruction, according to Schwarz, was a carcinoma of the gastro-enterostomy ring. Metastases to adjacent lymph glands and to the peritoneum were also noted. A Braun anastomosis was performed and was followed by rapid improvement. The patient was convalescing at the time the report was rendered, and no subsequent communication has appeared. A second instance of carcinoma in the line of union of the stomach and jejunum was mentioned by Hurst and Stewart,[2] without any accompanying clinical history or description.

A third case was reported rather recently by Eichelter.[3] A man of 55 had a partial gastrectomy (Billroth II) performed for chronic penetrating

* Submitted for publication, June 25, 1931.

* From the Department of Medicine of the University of Illinois College of Medicine and the Department of Pathology of the Cook County Hospital.

1. Schwarz, in discussion of Lengemann: Operationsbefunde an Gastroenterostomierten, Zentralbl. f. Chir. **53**:3000 (Nov. 20) 1926.

2. Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, London, Oxford University Press, 1929, p. 429.

3. Eichelter, G.: Spontanperforation des paralytisch erweiterten Duodenal-Schenkels 4 Jahre nach subtotaler Magenresektion wegen Ulcus (primäres Karzinom an der Anastomosenstelle), Deutsche Ztschr. f. Chir. **222**:106, 1930.

ulcer. He remained well for three and one-half years; then abdominal symptoms reappeared. When he came under the observation of Eichelter, at the age of 59, he was suffering from symptoms of a perforative peritonitis. Operation disclosed a nodular tumor at the anastomosis, dilatation of the proximal loop and acute rupture of a distention ulcer in the duodenum. Duodenojejunostomy and jejunostomy were performed. Shortly thereafter the patient died. Autopsy showed the gastro-enterostomy stoma to be narrowed by a firm, infiltrative growth, which microscopically proved to be an adenocarcinoma. The mucosa in the region of the anastomosis showed thickened folds and tumor formation. One of the mucosal swellings projected into the narrowed mouth of the proximal loop. Several metastases were found in the liver and esophagus and in a few peripancreatic lymph glands. The diagnosis of simple ulcer made at the time of the original operation in 1925 was confirmed by further study of the previously resected lesion. Eichelter concluded that the carcinoma had its point of origin in the anastomosis.

A fourth case, which constitutes the basis of this communication, presents a number of interesting features that appear to warrant a rather detailed report.

REPORT OF CASE

J. W., a white man of 52, entered the Cook County Hospital for the first time on March 14, 1929, with gastro-intestinal complaints ascribed to a suspected gastrojejunal ulcer. He related that he had suffered periodically from epigastric distress and heartburn from 1900 until the early part of 1918, when an appendectomy was performed. No relief followed. In June of the same year, he consulted and was operated on by Dr. N. M. Percy, who gave me a complete operative report. The laparotomy disclosed a duodenal ulcer, a chronic cholecystitis and extensive perigastric adhesions. The operative procedures included pylorectomy, with posterior gastro-enterostomy, cholecystectomy and division of the adhesions. For a year following laparotomy, the patient felt entirely relieved of his previous symptoms. After this time, he began to suffer from a recurrence, which led him to attend a dispensary, where he was treated at irregular intervals, with indifferent results.

At the time of entrance into the hospital, postprandial pain, bloating, acid eructations and an occasional attack of vomiting were the presenting complaints. The physical examination disclosed nothing of value. An Ewald meal returned no free acidity and 13 degrees of combined acidity. The test for occult blood on the gastric contents was positive. The chemical test for blood in the stool, which proved positive prior to treatment, subsequently became negative. The roentgenologic report indicated a well functioning gastro-enterostomy, with no evidence of ulcer. On Sippy management, the patient improved greatly but continued to belch. He was discharged on April 1, 1929, and immediately returned to his usual occupation.

The patient was not heard from until Oct. 7, 1929, when he reentered the hospital on account of severe lumbar pain and systemic manifestations of sepsis. An osteomyelitis involving the twelfth dorsal and first lumbar vertebrae was demonstrated and a soft parts abscess subsequently incised and drained. After recovering from the lumbar abscess, the patient directed attention to his gastro-intestinal complaints. He stated that following discharge from the hospital in April, 1929 he remained fairly comfortable for from three to four months. After this period,

his former epigastric burning reappeared one hour after meals. As time went on, the interval between food-taking and the occurrence of distress became shorter and shorter until at the time of his second admission it was usually less than fifteen minutes. Alkalis afforded but partial relief.

Physical examination disclosed, in addition to a considerable loss in weight, an egg-sized, circumscribed mass located in the epigastrium. The mass moved with respiration and was not tender. Repeated Ewald meals yielded no free acid and a total that varied between 6 and 10 degrees. The maximum quantity of material regained by aspiration was 60 cc. The test for occult blood on both the gastric contents and the stool was persistently positive. A roentgen examination made on Oct. 29, 1929, showed a filling defect on the greater curvature in the distal third of the stomach, and a gastro-enterostomy stoma that functioned moderately well.

Fig. 1.—Roentgenogram showing the filling defect on the greater curvature side of the distal third of the stomach.

The roentgenologist, Dr. C. H. Warfield, suggested the diagnosis of carcinoma of the gastrojejunal stoma.

The patient continued to suffer from postprandial epigastric burning, which was consistently aggravated by alkalis. Hydrochloric acid afforded some amelioration. In addition to the burning, the patient complained of a hunger pain, which occurred before meals and at night and was generally relieved by food. Two additional roentgen examinations demonstrated the same defect (fig. 1) that had been noted previously. The distress increased in intensity and persistency until the patient finally consented to submit to an operation. Accordingly, on Feb. 6, 1930, a laparotomy was performed by Dr. R. W. McNealy. There was evidence of a previous pylorectomy and posterior gastro-enterostomy. In the region of the anastomosis a soft, irregular mass was felt. There were no enlarged glands in the vicinity and

no demonstrable tumor nodules in the liver. The enterostomy was unhooked and the portion of stomach containing the tumor mass resected. The defect in the jejunum was then united to the lower end of the gastric opening (Billroth II). Following operation, the patient vomited fresh and clotted blood. A blood transfusion and coagulants failed to check the hemorrhage, and on Feb. 8, 1930, two days after operation, the patient died. Permission for autopsy was not granted.

Gross Description of Tumor.—The specimen consisted of a resected sleevelike portion of the stomach that measured 3 and 6 cm. along the lesser and greater curvatures, respectively. The distal end had been long since surgically closed. The diameter of the proximal opening was 8 cm. The mucosa in the region of the

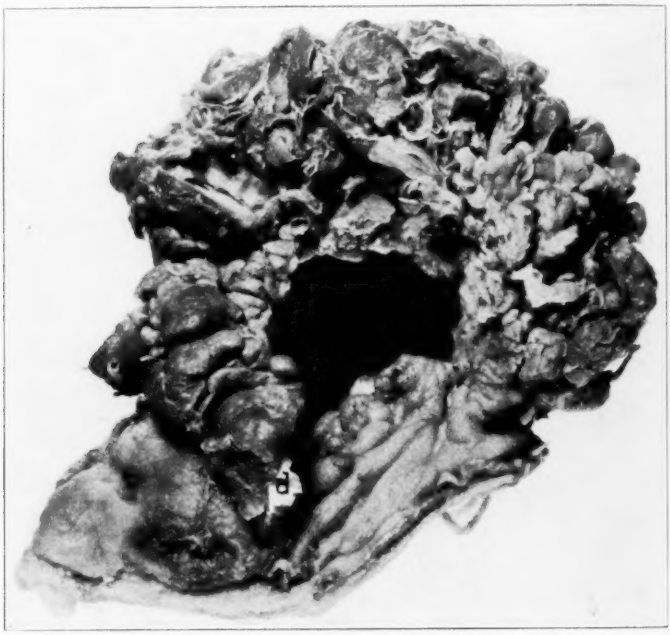

Fig. 2.—Polypoid tumor involving approximately three fourths of the circumference of the gastrojejunal stoma (seen from the gastric side). The histologic material for figure 3 was obtained from the right border of the defect (*d*).

proximal opening was relatively normal. In approaching the gastro-enterostomy, the mucosa was seen to be thickened and somewhat mammillated. Occupying the region of the distal stoma was a polypoid mass (fig. 2), which apparently had its point of origin in the margin and encircled about three fourths of the opening. The tumor was crescentic in form, the widest portion being near the greater curvature side, where it measured 6 cm. The narrowest portion of the tumor was located near the lesser curvature, in the region of which it possessed a width of 2 cm. The tumor consisted of closely set polyps of approximately uniform length but of variable thickness. The polyps that projected from 1.5 to 2 cm. above the surface of the surrounding mucosa were from 2 or 3 mm. to 2 cm. thick. The thin polyps had slender pedicles whereas the thicker polyps were for the most part sessile.

Cross-section of the gastric wall permitted differentiation of the individual coats. The mucosa exhibited a moderate thickening and demonstrated polypoid projections composed of a relatively homogeneous, white tumor tissue. The submucous layers were unchanged except for moderate thickening of the muscular coat. In the region of the lesser curvature was a strip of tissue 3 cm. broad which was free from the aforementioned luxuriant pediculated growth. The mucosa here, however, was not smooth, but presented discrete, oval and round elevations, from 3 to 8 mm. in diameter, projecting from 2 to 4 mm. above the surface of the normal mucosa.

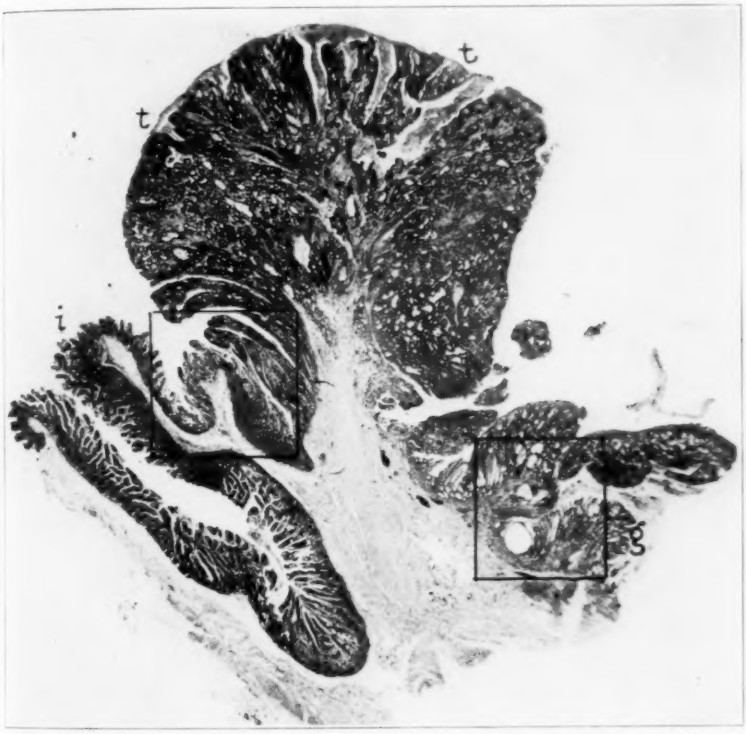

Fig. 3.—A section taken radial to the axis of the stoma to include intestinal mucous membrane (*i*), tumor tissue (*t*) and gastric wall (*g*); × 7.

Cross-section of the gastric wall in this region showed the excrescences to be sessile, mushroom-like thickenings of the mucosa without extension into the subjacent layers.

Microscopic Report.—The most informative sections were the radial ones taken through the ring of polypoid tumor tissue to include parts of the adjoining jejunal and gastric walls (fig. 3). On the intestinal side, the mucous membrane was thrown into delicate folds (valvulae conniventes), which exhibited the characteristic crypts of Lieberkühn, containing numerous goblet cells (fig. 4). Except for an increased

number of cellular elements in the tunica propria, no significant abnormality of the intestinal mucosa was noted.

In approaching the polypoid overgrowth there was a rather abrupt transition (fig. 4) from the relatively normal intestinal mucous membrane to an atypical papillary structure, which presented the characteristics of a neoplasm. The newly formed tissue (fig. 5) consisted mainly of acini, which were irregular in size, form and arrangement. The glands were generally lined by a single layer of columnar epithelium having no specific characteristics. In places, the lining cells assumed a

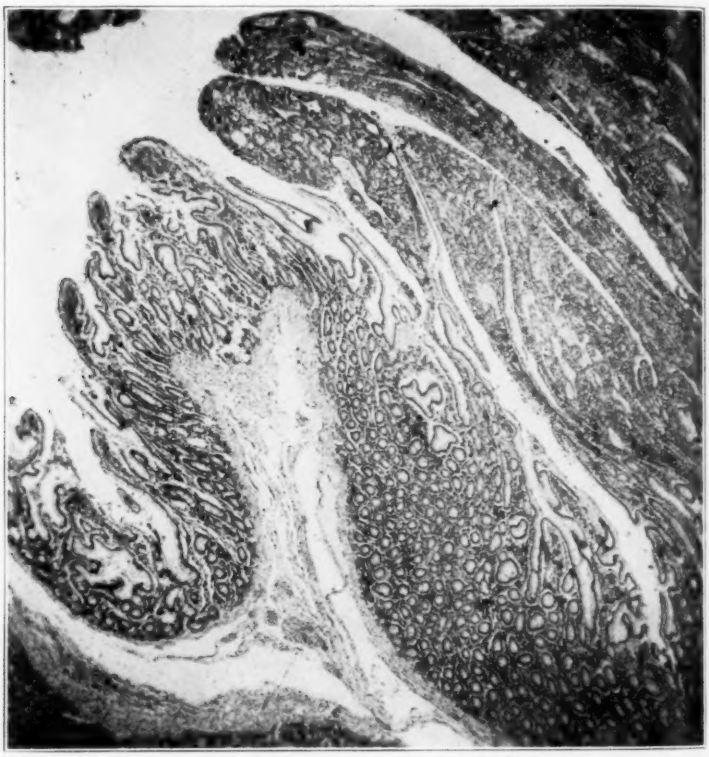

Fig. 4.—A higher magnification of the region indicated in figure 3 to demonstrate the transition from a relatively normal intestinal type to a neoplastic type of tissue; × 35.

cuboidal form. There was a lack of uniformity in the relationship of the epithelial cells to one another. A moderate variation in size, shape, polarity and chromatin content of the individual cells was noted. Mitotic figures were encountered rather frequently. The lumina of the atypical glands contained varying quantities of precipitated albumin and cellular elements, including macrophages filled with lipoid droplets, polymorphonuclear leukocytes and round cells. The interglandular supportive tissue was edematous and densely infiltrated by cells similar to those noted within the acini. In some areas, the lipophages were extremely numerous, whereas

in other areas the accumulations of polymorphonuclear leukocytes were particularly thick.

The transition from the papillary growth described to the nonneoplastic gastric mucous membrane (fig. 6) was a gradual one. In approaching the latter, there was encountered a zone in which the glands in the deeper layers were gastric in type and typical in character, whereas those in the superficial layers were indifferent in type and atypical in character. In passing further, the glands that were of the

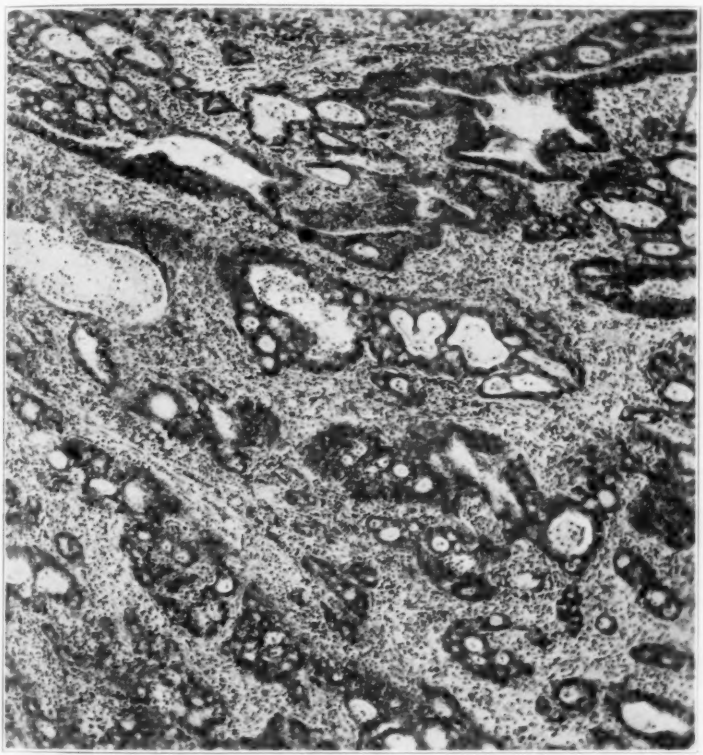

Fig. 5.—A higher magnification of an area in the polypoid tumor (fig. 3 *t*), illustrating the anaplastic character of the growth; × 80.

pyloric type assumed a relatively normal appearance, except for cystic dilatations and minor distortions. In the tunica propria of this area there were dense infiltrations of round cells and macrophages. Sections from different portions of the tumor exhibited essentially the characteristics described. However, in some areas, the papillary nature of the growth was much more pronounced than in the portion illustrated in figure 3. There was also a wide variation in the number of polymorphonuclear neutrophils present, for in some sections the leukocytes were densely accumulated whereas in others there were few.

In sections from the flat papillomas located near the stoma, different types of proliferated glands were noted. In some preparations, the glandular structures were of normal appearance, whereas in others the neoplastic character described in connection with the polypoid overgrowth was noted. Transitions between the two kinds of glands were commonly encountered. For instance, in the same section one found crypts and tubules that were relatively normal in appearance and others that were somewhat irregular and bizarre in configuration. The cells lining the

Fig. 6.—A higher magnification of the transition zone (indicated in fig. 3) between gastric mucous membrane, the seat of a catarrhal inflammation, and the adenocarcinoma; × 35.

atypical structures were frequently polymorphous and possessed hyperchromatic nuclei. The degree of anaplasia of these crypts and tubules was insufficient to justify an unqualified diagnosis of carcinoma, as infiltrative and destructive properties were not demonstrable. However, the lack of uniformity and the atypical appearance of the glands and individual cells suggested a "precarcinomatous" state. Each of these papillomatous nodules appeared to constitute an independent tumor, since no connection between them was demonstrable.

The mucous membrane in the region of the aforementioned papillomas had a variegated appearance. There were areas where the tubules were greatly reduced in number, being replaced by dense infiltrations of round and plasma cells, macrophages and polymorphonuclear leukocytes. In other areas, there were flat and polypoid prominences made up of closely set proliferated glands. Cystic dilatations were in places quite prominent, as were also wide and irregular gastric pits. A number of the epithelial cells covering and lining these pits had undergone goblet cell metaplasia. The muscularis mucosae was thickened and densely infiltrated by inflammatory cells.

COMMENT

The reappearance of symptoms following gastro-entero-anastomosis for peptic ulcer generally indicates a benign complication or sequel. Recurrence of the old or formation of a new ulcer and nonmalignant obstruction are most frequently suspected. Occasionally, however, the clinical manifestations may be produced by a carcinoma. In one such case, that of Schwarz,[1] a patient who had remained well for six years after gastro-enterostomy developed symptoms of obstruction of the stoma, which were due to a malignant growth. In another case, that of Eichelter,[3] a neoplasm by encroaching on the lumen of the stoma led to manifestations referable to obstruction of the proximal loop. In a third case, the one herein reported, the carcinoma, being polypoid, produced no clinical obstruction, but gave rise to a set of indistinctive symptoms. The presence of a palpable mass and the roentgen evidence of a filling defect within the gastric silhouette furnished the chief reasons for the preoperative diagnosis of carcinoma of the anastomosis.

The main point of interest centers about a possible causal relationship between the presence of a gastro-enterostomy and the development of a carcinoma. In other words, does a gastro-enterostomy determine in any way the occurrence of a malignant growth, or is the coexistence an accidental one? In the case reported by Schwarz,[1] observations with regard to the tumor were limited to the palpation of a mass at the stoma and the presence of metastases in the adjacent lymph glands and the peritoneum. There was no opportunity for further observation, as excision was not attempted at operation and the patient was still alive when the publication appeared. Whether or not the neoplasm originated in the anastomosis and was actually related to it cannot be ascertained from the facts available. The case of Hurst and Stewart [2] sheds no light on the problem as no description of the tumor accompanies the report. In Eichelter's [3] case, the communication does not include facts that are most pertinent to the question of a causal relationship. The statement that the gastric mucosa at the anastomosis showed thickened folds and tumor formation is suggestive of a hypertrophic gastritis, which may be considered a forerunner of carcinoma (see a later paragraph). Unfortunately for present purposes, the main theme of the paper is the duodenal obstruction, and the gross and microscopic aspects of the new growth are slighted. From the information obtained in Eichelter's

report it would be difficult to establish any relationship between the artificial stoma and the development of the malignant growth. In the case herein described there appears to be adequate evidence to suggest that the occurrence of the carcinoma at the new stoma was determined by the gastro-enterostomy.

There is a growing tendency on the part of pathologists to consider inflammatory hyperplasia, polyposis and carcinoma as merely stages of one pathogenic process. The three types of proliferation are frequently coexistent and accompanied by transitional stages that denote almost unequivocally the development of one from the other. In the stomach, particularly, is the association of inflammatory hyperplasia, adenomatous polyps and polypoid carcinoma a relatively common one. The evidence pointing to a direct relationship between chronic gastritis and carcinoma of the stomach is most convincing. The literature and personal observations indicating the precarcinomatous nature of chronic inflammatory changes in the stomach have been splendidly presented by Konjetzny,[4] to whose works the reader is referred for more detailed information.

If it is true that chronic gastritis may lead to carcinoma (in a predisposed subject), the malignant growth at the stoma in the case reported here can be reasonably associated with the gastro-enterostomy. The histologic sections demonstrate the presence of chronic inflammatory changes of high grade in the gastric mucous membrane about the anastomosis. Presumably the gastritis was the result of abnormal mechanical and chemical insults due to the altered physiology conditioned by the operation. In addition to the atrophic-hyperplastic changes which constituted part of the gastritis proper, there were a number of frankly benign sessile and pediculated polyps. There were also small polypoid growths that contained atypical structures and cells suggestive of "precarcinomatous" proliferation and others that were frankly malignant. Transitions from inflammatory hyperplasia to benign neoplastic overgrowth and from benign to malignant hyperplasia could be readily identified. The presence of several independent carcinomatous polyps also favors the view of an inflammatory etiology, since a multicentric origin is, according to Konjetzny [4] and others, characteristic of a malignant condition developing from a chronic gastritis. The occurrence of the large polypoid mass just at the stoma is explained by the circumstance that the site of anastomosis was subjected to the maximum injury and was therefore the first to undergo inflammatory and subsequent malignant changes. Whether or not a pyloric carcinoma would have developed had no gastro-enterostomy been performed is open to conjecture.

4. Konjetzny, G. E., in Anschütz, W., and Konjetzny, G. E.: Die Geschwülste des Magens, Deutsche Chirurgie, Stuttgart, F. Enke, 1921, pt. 46, first half, no. 1, p. 26; Die entstehungsgeschichtlichen Beziehungen der Gastritis zum Karzinom, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 4, pt. 2, p. 904.

THE EFFECT OF PROLONGED DISTENTION OF THE STOMACH IN DOGS *

J. PAUL BURGESS, M.D.

HORACE G. SCOTT, M.D.

AND

A. C. IVY, M.D.

CHICAGO

The mechanism concerned in the production of acute dilatation of the stomach is not fully understood. Numerous theories have been advanced to account for it, but none has been entirely adequate. The reason is perhaps to be explained by the fact that this condition may be brought about in several different ways.

When first described by Brinton [1] it was thought to be primarily a passive phenomenon of a purely paralytic nature. Conner [2] stated: "The absence in almost all cases of obvious obstruction at the pylorus, and the fact that a similar paralytic distention of the intestines is a not uncommon phenomenon after abdominal operations and in peritonitis served to support this view as has also the experimental work of Carion and Hallion." [3] The latter investigators said that "after resection of both nerves (vagi) above the diaphragm we have seen produced in the dog an enormous dilatation of the stomach and of that portion of the esophagus innervated."

The occurrence of acute dilatation of the stomach after section of the vagi, however, is quite rare, since many investigators who have performed this operation in animals have failed to observe it, although they have consistently found a change in gastric peristalsis.[4] Ivy,[5] working on dogs, and Patterson,[6] on lower animals, found on making actual measurements that the postural tone of the stomach is decreased after section of the gastric vagi for a period of several days, that is, more

* Submitted for publication, June 29, 1931.

* This investigation has been aided by a grant from the Josiah Macy, Jr., Foundation.

* From the Department of Physiology and Pharmacology, Northwestern University Medical School.

1. Brinton, quoted by Conner: Am. J. M. Sc. **133**:345, 1907.
2. Conner: Am. J. M. Sc. **133**:345, 1907.
3. Carion and Hallion, quoted by Conner (footnote 2).
4. Cannon: Am. J. Physiol. **29**:250, 1911. Carlson: ibid. **32**:369, 1913.
5. Ivy, A. C.: Physiology of Stomach: Studies on Gastric Ulcer, Arch. Int. Med. **25**:6 (Dec.) 1920.
6. Patterson, T. L.: Am. J. Physiol. **49**:147, 1919; ibid. **53**:293, 1920.

air was necessary to produce a certain intragastric pressure after section of the vagi than before. Loss of vagus tone may be a contributing factor, but not a prime or sole factor.

In the early part of the twentieth century, numerous investigators, among them Conner, felt that "the most important single cause of such stomach dilatation is the sudden incarceration of the duodenum between the root of the mesentery which passes in front of it and the vertebral column behind." For a time this condition was widely discussed in this country and elsewhere and became known in the literature as arteriomesenteric occlusion. More recently, however, numerous investigators have observed acute dilatation to occur within a few minutes or even seconds during the course of an abdominal operation, right under the very eyes of the operator. These occurrences have led to a belief that dilatation may be an active and not a passive phenomenon. This rapid accumulation of gas within the stomach has been due undoubtedly to some process that has shut off the oropharynx from the laryngopharynx and has brought about an expiration of air from the lungs and trachea into the esophagus and stomach. The possibility of this occurrence has been studied recently by McIver [7] on experimental animals. He came to the conclusion that "the distinguishing feature of acute dilatation occurring under general anesthesia is an active one and not a passive phenomenon. The gas responsible is atmospheric air." Just why this air is diverted into the stomach and not into the nasal passages he does not attempt to say.

However, regardless of the mechanism that may produce dilatation of the stomach, the resulting symptoms are quite similar once this condition obtains. The immediate effects are only slight, but if the distention is prolonged over several hours or days the symptoms become very grave, and death will frequently occur unless this condition is promptly relieved.

The cause of death, like the mechanism producing dilatation, has never been adequately explained.

The literature contains the reports of numerous cases of patients who have died from prolonged distention of the stomach. There have been numerous theories advanced to explain the cause of death just as there have been to explain the mechanism producing the distention, and the reason for so many theories is probably the same, namely, there are undoubtedly numerous factors that play a rôle in the production of the fatal outcome. In view of the recent work on the cause of death in simple high intestinal obstruction, the rapidly fatal effects of dilatation have been attributed to similar causes, among them the loss of chlorides in the gastric juice, the loss of fluids and essential intestinal juices such

7. McIver, M. A.: Ann. Surg. **85**:704, 1927.

as bile and pancreatic juice coupled with a failure of the organism to obtain nutritive materials and fluids. Undoubtedly these factors play an important rôle in the cause of death. However, the paper of Conner[2] emphasizes the serious nature of acute dilatation of the stomach and the rapidity with which death ensues unless it is relieved. Further, the pathologic reports included in Conner's paper point out the fact that the stomachs of patients dying of this condition manifest gross and microscopic changes. These changes in the stomach are probably the result of the disturbance of the circulation of the gastric wall and, we feel, may play an important rôle in the fatal outcome. This possibility, we believe, has been overlooked in recent years in view of the emphasis that has been placed on the loss of chlorides in the gastric secretion. But so far as we have been able to find, no one has studied the effects of prolonged distention of the stomach per se.

We thought that the effects of distention of the stomach per se might be studied by placing a large balloon into the stomach by means of gastrostomy and then distending it with water, a procedure that would prevent the loss of water and chlorides through vomiting and hence avoid this complicating factor. Also, since distention of the stomach may directly or indirectly affect the heart, which condition might be one of the factors concerned in the cause of death from dilatation of the stomach, electrocardiograms were made before and during the period of gastric distention.

EXPERIMENTAL METHODS

We performed gastrostomies on twelve dogs under sterile technic. A large rubber balloon was inserted into the stomach immediately after gastrostomy and was then inflated with varying amounts of water. Enough water was introduced (from 500 to 700 cc.) initially to prevent any leakage of gastric juice through the fistula. The balloons were further distended at intervals over periods ranging between twenty-two and seventy-two hours. The total amount introduced varied somewhat with the size of the dog, or varied between 1,200 and 2,250 cc. This amount of fluid was used with the idea in mind that it is about twice the amount of milk that a dog of this size would voluntarily ingest when hungry. Dogs weighing from 15 to 30 pounds were used. Electrocardiograms were made on seven dogs before and at intervals after distention.

RESULTS

The distention of the stomach resulted in the death of all the twelve dogs in from twenty-six to ninety hours. In all the dogs the distention caused retching at the time the fluid was first introduced, but none of the dogs was able to vomit and therefore could not lose fluids and chlorides in this manner. After the first period of retching the animals became more or less adapted to the distention and either did not retch subsequently or only infrequently. Most of them salivated, which

denotes that the nausea-salivary mechanism was probably continuously excited. No fluid was lost via the fistula, except in two instances in which the balloons were ruptured during the night; when this happened a new balloon was introduced and distention again produced. None of the dogs developed diarrhea. An excess of fluid (from 200 to 250 cc.) was present at autopsy in the lumen of the intestine in five instances and was present chiefly in the duodenum and stomach.

Blood chlorides were determined in seven of the dogs (dogs 5, 8, 9, 10, 11, 13 and 14), the Van Slyke method being used. Only a very slight fall occurred in six of the seven dogs, the last blood chloride in milligrams per hundred cubic centimeters of blood taken prior to death being dog 5, 430; dog 8, 316; dog 9, 480; dog 10, 430; dog 11, 442; dog 13, 442, and dog 14, 435. The urine was scanty.

Electrocardiograms were made prior to the distention and daily in most cases thereafter on seven dogs. The distention caused a marked acceleration of the heart rate and a disappearance of the sinus arrhythmia which is normally quite marked in dogs. The T wave was negative before distention in six of the seven dogs. Distention caused it to become negative in one dog (no. 5) in which it was positive, and markedly accentuated its negativity in the others. The Q wave was uniformly accentuated. The electrocardiograms of dog 5 are particularly interesting in that there was some evidence of abnormal auricular activity prior to distention as shown by the occurrence of an occasional "ectopic auricular contraction" (?) and a notching or slurring of the P wave. Two and one-quarter hours after distention was induced, the suspected ectopic contraction became very evident, being positive in lead 1, diphasic or negative in lead 2 and negative in lead 3. It was regular and of the same voltage as the P wave. Twenty-four hours later the ectopic wave was negative in lead 1. In leads 2 and 3 an occasional ventricular complex was present (fig. 1, 2 and 3). Other occasional irregularities were present in the electrocardiograms which were difficult to interpret.

After the preliminary period of retching, the dogs gradually became more and more depressed, listless and weak and died in coma without muscular twitchings or convulsions.

Autopsy was performed on some dogs immediately after death, and on those dying during the night, it was performed early the next morning. There was no evidence of peritonitis in any of the dogs, with the exception of dog 6 in which there was some question, and in dog 10 in which a gas bacillus infection was present in the wall of the duodenum. Serosanguineous fluid was present in the peritoneal cavity of nine of the twelve dogs. The stomach was markedly distended in all the dogs, as might be expected, as was also the case in dog 14 in which the balloon was found to be ruptured at autopsy. This distention of the stomach

involved the pyloric antrum, which was usually not distended by the balloon. The stomach wall was markedly thinned out, and in practically every dog mucosal, submucosal and subserous hemorrhages were present. Hemorrhagic erosions of the stomach were present in some of the dogs. The entire intestine was dilated in three (dogs 2, 5 and 9), the duodenum in two (dogs 3 and 10) and the duodenum and jejunum in one (dog 8). The intestine was either not distended or contracted in six dogs (dogs 1, 4, 6, 11, 13 and 14), the ileum was contracted in one (dog 8) and the ileum and jejunum were normal in one (dog 10). The superior mesenteric vein and the splenic and pancreaticoduodenal veins were always distended, frequently markedly so. The stomach and duodenum were usually markedly congested and discolored. The spleen and pancreas were congested as a rule. Fat necrosis was observed in two dogs. In four dogs the lungs were congested, but otherwise negative.

PROTOCOLS

Only a condensed protocol of each of the twelve experiments will be given. Autopsy records and complete analysis of electrocardiograms will not be included because of lack of space.

Dog 1.—Distention of the stomach was produced by introducing 2,000 cc. of water over a thirty-four and one-half hour period into a large rubber balloon placed in the stomach by means of gastrostomy. Death ensued within the next twenty-four hours.

Dog 2.—Distention was produced as in dog 1, 1,500 cc. of water being introduced over a twenty-two hour period. Death ensued in thirty-six and one-half hours.

Dog 3.—Distention was produced as before, 2,250 cc. of water being introduced over a seventy-two hour period. Lethal issue occurred in approximately ninety hours.

Dog 4.—Distention was produced as before, 2,250 cc. of water being introduced over a period of sixty-five hours. Death occurred in eighty-five hours.

Dog 5.—Distention was produced as in the other experiments. Predistention blood chlorides ranged from 450 to 460 mg. per hundred cubic centimeters of blood. The balloon was distended with 1,750 cc. of water over a twenty-four hour period. The blood chlorides fell to 430 mg. The dog then pulled the balloon out. Redistention began six days later. The balloon was distended with 2,250 cc. of water over a forty-eight hour period. The dog died during the next twelve hour period.

Electrocardiograms taken prior to the first distention showed an inverted T wave in lead 1. On distention, in lead 1 the T wave was inverted; in lead 2 and 3 it was notched and the Q wave was exaggerated. The P wave was distinct, but was occasionally immediately preceded by an irregular ectopic contraction of low voltage. We could not be certain whether this effect was cardiac or somatic. After twenty-four hours of distention, the T wave was positive in all leads with a slight notching at its apex. The heart rate was 280 per minute. The balloon was pulled out by the dog, and six days later an electrocardiogram was made. Lead 1 showed a small diphasic or inverted T wave (fig. 1, *A1*). In lead 2, the

T wave was positive (fig. 1, *A2*). In lead 3, the P and T waves were notched occasionally, owing to an occasional ectopic contraction of the same voltage as the P wave. The balloon was inserted and distended with water. Two and one-quarter hours later a rhythmically occurring ectopic contraction was present in lead 1 (fig. 2, *B1*) and the T wave was positive. In leads 2 and 3 the same abnormality was present, but was negative (fig. 2, *B3*) in lead 3. The ectopic contraction had no effect on the ventricle and its rhythm followed the sinus arrhythmia. Twenty-four hours later lead 1 showed a negative (fig. 3, *C1*) rhythmical ectopic contraction. In leads 2 and 3 the ectopic contraction was positive (fig. 3, *C2* and *C3*) and an occasional "ventricular complex" (?) occurred.

Dog 6.—Distention was produced as in the other dogs, 2,000 cc. of water being introduced into the balloon within the twenty-two hour period. The dog died twenty-six hours after the dilatation was begun.

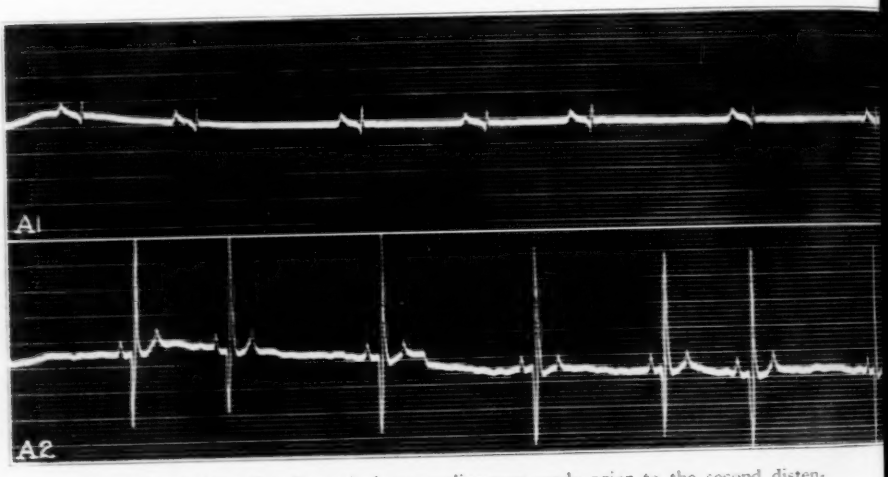

Fig. 1 (dog 5).—Control electrocardiograms made prior to the second distention. Note in lead 1 (*A1*), the diphasic or inverted T wave and in lead 2 the positive T wave.

Dog 8.—Distention was produced. Electrocardiograms and blood chloride determinations were made before the onset of dilatation of the stomach. The blood chlorides ranged from 475 to 490 mg. per hundred cubic centimeters of blood. Control electrocardiograms (fig. 4, *A*) showed a cardiac rate of from 60 to 80 per minute with a marked sinus arrhythmia. There was a diphasic or negative or diphasic T wave in all three leads. Subsequent studies on other supposedly normal dogs showed this same phenomenon of a negative T wave quite frequently.

Distention of the stomach with 2,000 cc. of water over a five hour period gave a markedly negative declination of the T and Q waves in leads 2 and 3 (fig. 4, *B*). The heart rate was accelerated appreciably and the arrhythmia abolished. The dog then pulled the balloon out during the night. Redistention was not begun again until three days later, when the blood chlorides were found to be 430 mg. Control electrocardiograms at this time showed a rate of 140 with a slight sinus

arrhythmia. The T wave was inverted in all three leads (fig. 4, *C* and *D*). Redistention was begun; 1,500 cc. of water was introduced during the afternoon. Electrocardiograms taken five hours after the onset showed a marked acceleration of heart rate with abolition of the sinus arrhythmia and a very marked accentuation of the negative T wave (fig. 4, *E*). The balloon was found ruptured the next morning. The blood chlorides were the same. Electrocardiograms revealed a rate of 90 per minute with a reappearance of the sinus arrhythmia. The T wave was broadened and was again dichrotic. The increase in voltage was to be noted and the appearance of a Q wave in lead 1. The balloon was redistended during the morning and afternoon with 1,750 cc. of water. The blood chlorides were 320 mg. at 5 p. m. Electrocardiograms taken the following day at 2 p. m., i. e., twenty-eight hours after distention, with 2,250 cc. of water in the balloon, revealed a marked tachycardia with a moderately accentuated negative T wave in all leads

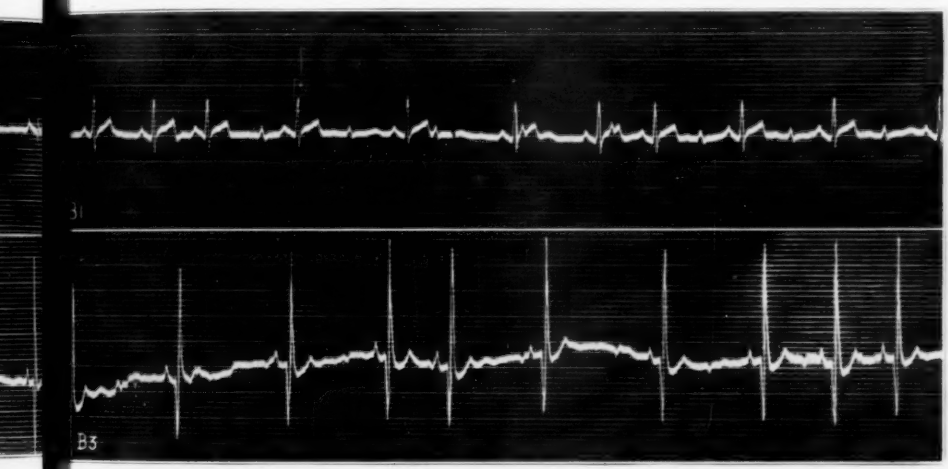

Fig. 2 (dog 5).—Electrocardiograms made two and one-quarter hours after distention of the stomach. Note that the T wave is positive and that there is a rhythmically occurring ectopic contraction. Measurements show that it is influenced by the sinus arrhythmia. The ectopic contraction is negative in lead 3 (*B3*).

(fig. 4, *F*). An occasional complex occurred which was difficult to interpret. The blood chlorides at this time were 316 mg. The dog was alive at 11 p. m. thirty-seven hours after the onset of the third distention, but died some time before 8 a. m.

Dog 9.—Distention was produced as in the other dogs. Predistention blood chlorides were 520 mg. The electrocardiogram was normal except for sinus arrhythmia and an inversion of the T wave. Distention was begun at 12 noon: 1,200 cc. of water was introduced by 4 p. m. The blood chlorides at 4:30 p. m. were 480 mg.; electrocardiograms showed a disappearance of the arrhythmia and a marked acceleration in rate. The dog was found dead at 8 a. m. the next morning.

Dog 10.—Distention was produced as before. Predistention blood chlorides ranged between 470 and 474 mg. per hundred cubic centimeters of blood. Electro-

cardiograms showed a rate of 110 and a QRS complex of low amplitude. The T wave was inverted in leads 2 and 3 and flattened in lead 1. Distention was produced with 1,000 cc. of water all at one time, i. e., approximately twenty minutes were required to introduce it. When between 700 and 800 cc. had been inserted, the dog retched some. Twenty-four hours later 500 cc. more was introduced. Respiratory distress, frothing at the mouth and retching were noted. Electrocardiograms taken nineteen hours after distention showed more marked inversion of the T wave, abolition of the arrhythmia and a rather marked tachycardia. The blood chlorides twenty-four hours after the dilatation were 430 mg. per hundred cubic centimeters. The dog died within thirty-six hours of the onset of the experiment.

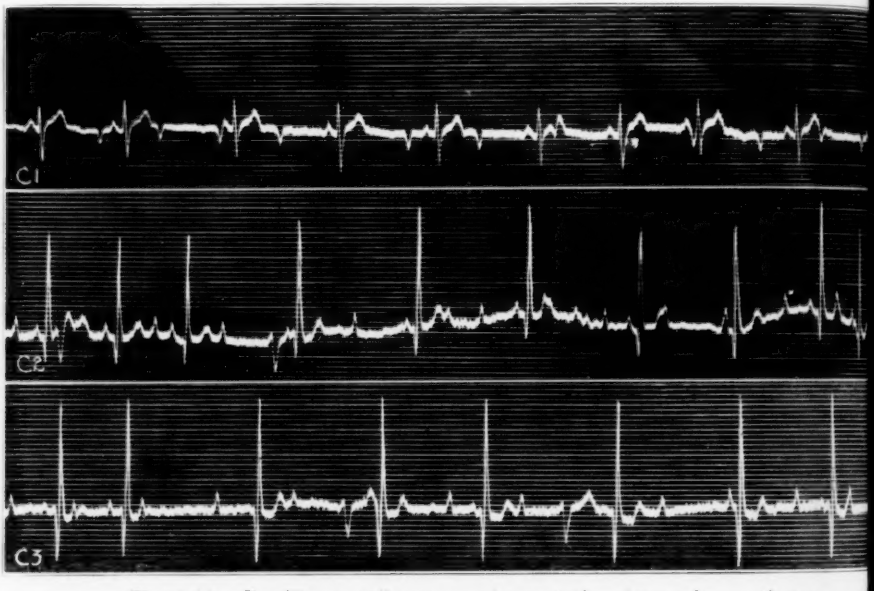

Fig. 3 (dog 5).—Electrocardiograms made twenty-four hours after continuous distention. Note the negative ectopic rhythmical contraction in lead 1 (*C1*) and that it is positive in lead 2 (*C2*) and lead 3 (*C3*). Lead 3 (*C3*) shows a "ventricular complex" that occurred occasionally.

Dog 11.—Distention was produced as in the other experiments. The dog was all brown with long hair. Predistention blood chlorides were 480 mg. Electrocardiograms showed a rate of 120 and a slight sinus arrhythmia. The T wave was inverted in all three leads (fig. 5, *A*). Distention was produced with 1,000 cc. of water. Retching occurred when 700 cc. had been added. Five hundred cubic centimeters was added first, then 500 cc. thirty minutes later. Electrocardiograms taken nineteen hours later showed a marked accentuation of the negative T wave, abolition of the arrhythmia and a marked acceleration of the cardiac rate (fig. 5, *B*). The blood chlorides twenty-four hours after distention were 442 mg. Five hundred cubic centimeters more of water was added. The dog died within thirty-six hours.

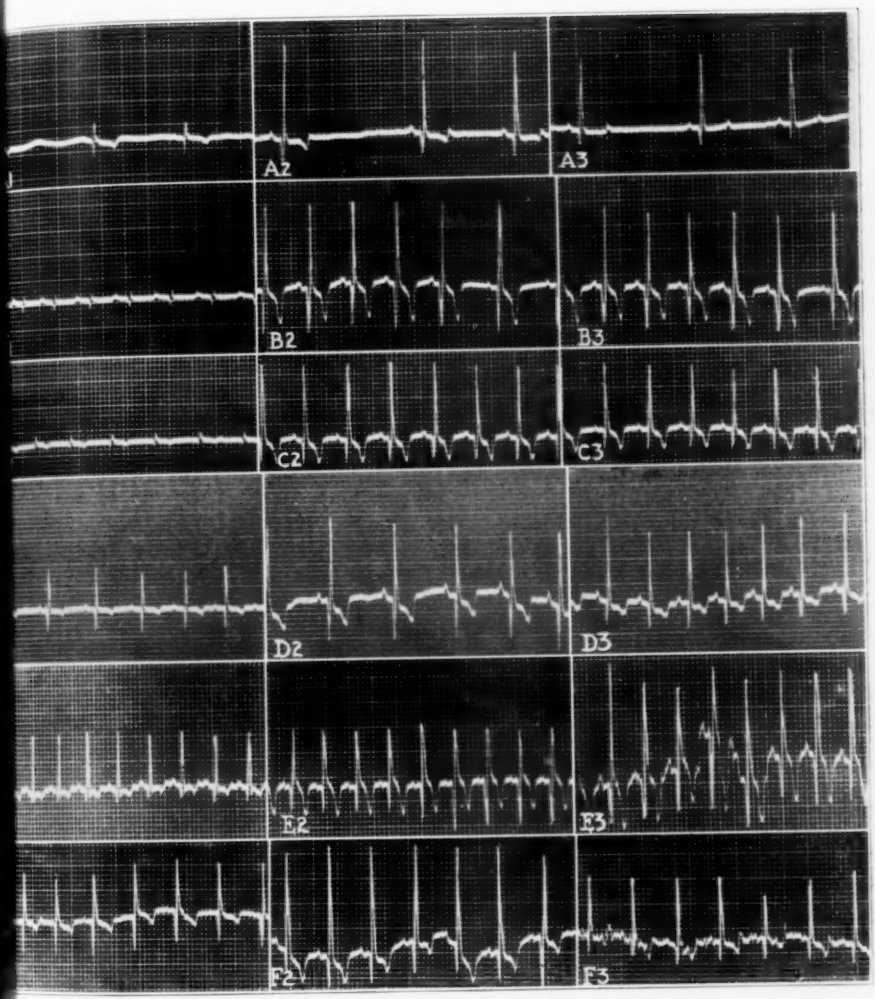

Fig. 4 (dog 6).—The A series is the control electrocardiogram. The B series was taken immediately after distention. Note the tachycardia and accentuation of the T wave. The balloon was pulled out. The C series was taken twenty-eight hours after the second distention, when the dog was quite sick. The balloon was pulled during the night. Series D was taken the following afternoon. Note the increase in voltage in lead 1 and that the tachycardia has persisted for from twelve to eighteen hours after release of distention. The stomach was distended again. Series E was taken twelve hours after the third distention. The balloon ruptured the next morning. An electrocardiogram was taken. Then the stomach was distended again, and twenty-eight hours later series E was taken. The dog died at thirty-seven hours.

Dog 13.—Distention was produced as in the other experiments. The dog was a white fox terrier. Predistention blood chlorides were 460 mg. per hundred cubic centimeters of blood. Electrocardiograms showed a rate of 90 with a negative T wave in all three leads (fig. 6, *A*) and a moderate sinus arrhythmia. One thousand cubic centimeters of water was introduced over a ten minute period. Nausea and retching were noted when 700 cc. had been introduced. Electrocardiograms taken nineteen hours after distention showed a rate of 240 per minute

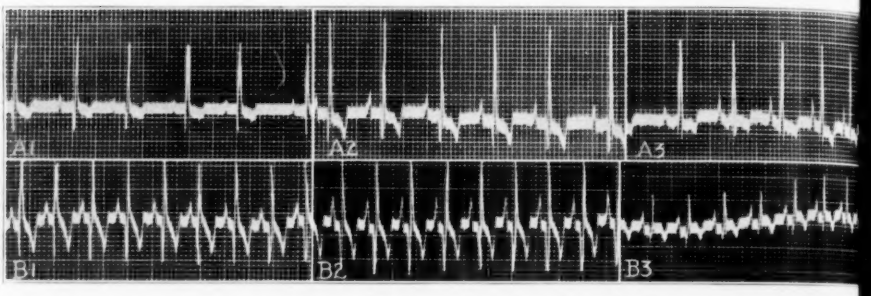

Fig. 5 (dog 11).—Series A is the control electrocardiogram. Series B was taken nineteen hours after distention.

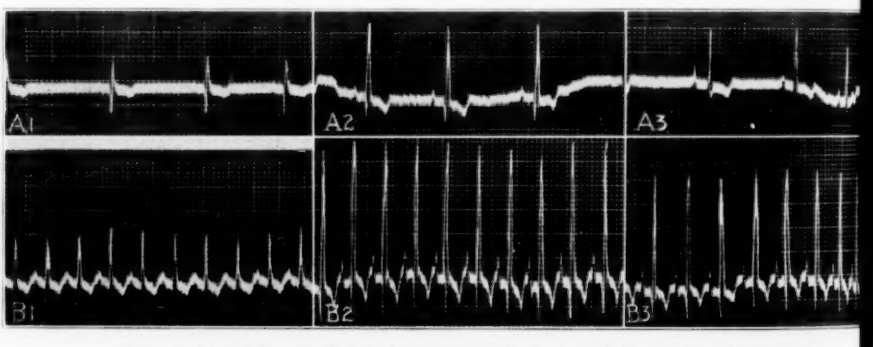

Fig. 6 (dog 13).—Series A is the control electrocardiogram. Series B was taken nineteen hours after distention.

with an abolition of the sinus arrhythmia. The T wave was negative in all three leads and moderately accentuated (fig. 6, *B*). The blood chlorides twenty-four hours after distention were 442 mg. per 100 cc. of blood. Five hundred cubic centimeters more of water was added. After the addition of 300 cc., dyspnea, frothing at the mouth and retching were noted. The dog died during the night, less than thirty-six hours after the onset of the distention.

Dog 14.—The dog was all brown, with long hair and a long tail. Predistention blood chlorides ranged between 476 and 509 mg. per hundred cubic centimeters. Electrocardiograms showed a rate of 100, a slight sinus arrhythmia, an inversion

of the P wave in lead 3 and an inversion of the T wave in leads 2 and 3. The negative T waves were rather marked. In lead 1 the T wave was positive. Distention was produced with 1,000 cc. of water over a fifteen minute period. Fifteen minutes later the dog vomited a small amount of frothy material. The balloon was found to be ruptured the next morning. Blood drawn for the chloride determination showed 457 mg. per hundred cubic centimeters. The balloon was reinserted and distended with 750 cc. of water. Slight respiratory distress and retching occurred during distention. Electrocardiograms taken immediately afterward showed a positive P wave in lead 3. There was a moderate tachycardia, and the sinus arrhythmia was abolished. Blood chlorides twenty-four hours after redistention were 433 mg. Electrocardiograms twenty-six hours after a second distention were quite similar to the previous electrocardiograms. The negative T wave was slightly more accentuated and the rate more rapid (180). The blood chlorides at thirty-one hours were 420 mg.; at forty-eight hours, 435 mg. Electrocardiograms at forty-nine hours showed a similar picture except that the negative T wave was not so marked. Two hundred cubic centimeters more of water was added at fifty hours. The dog died during the night, after living approximately sixty-five hours.

COMMENT

These results show that distention of the stomach per se may lead to changes that are sufficient to cause death in from twenty-six to seventy-two hours. The experiments being of such a nature that loss of chlorides and dehydration could not result from vomiting, these two factors may be ruled out as important in the cause of death in our experiments, and indicate that they are only contributory factors in the cause of death in acute dilatation of the stomach as it occurs clinically.

The changes at autopsy in these animals, although more severe, coincide for the most part with the pathologic changes in cases of acute dilatation of the stomach in man as reported by Conner.[2] The anatomic changes are those that one might predict to occur on the basis of an arteriomesenteric occlusion and of a blockage of the venous return by the increased intragastric pressure. These factors have been elucidated by the experimental work of Dragstedt and Dragstedt,[8] Van Zwalenburg,[9] Gatch, Trusler and Ayers,[10] and Dragstedt, Lang and Millet.[11]

Although we believe from the clinical picture that dogs with a distended stomach present some element of shock, we feel more certain that the chief cause of death is a toxemia that results from

8. Dragstedt, C. A., and Dragstedt, L. R.: Acute Dilatation of the Stomach, J. A. M. A. **79**:612 (Aug. 19) 1922.

9. Van Zwalenburg: Ann. Surg. **46**:780, 1907.

10. Gatch, W. D.; Trusler, H. M., and Ayers, K. D.: Effects of Gaseous Distention on Obstructed Bowel: Incarceration of Intestine by Gas Traps, Arch. Surg. **14**:1215 (June) 1927.

11. Dragstedt, L. R.; Lang, V. F., and Millet, R. F.: Relative Effects of Distention on Different Portions of the Intestines, Arch. Surg. **18**:2257 (June) 1929.

the absorption of toxic products from cellular trauma or destruction due to the disturbed circulation. This is shown by an experiment (Drs. Ivy and Burgess) in a dog in which pyloric obstruction was produced after section of both vagi and splanchnic nerves. Vomiting and death occurred but were delayed only about one day when compared to controls. Dragstedt and Dragstedt [8] stated that the symptoms of acute dilatation of the stomach, which often makes it difficult to distinguish this condition from intestinal obstruction, "are those of a severe toxemia rather than the result of reflex or mechanical effects from the stretched and dilated stomach." We agree with this statement and believe that the toxemia is due indirectly to the distention which produces such an obstruction to venous return that tissue damage and a disturbance of the normal phenomena of selective absorption result. The interference with venous return obviously embarrasses the circulatory mechanism, as is shown by the marked acceleration of the heart. In addition, the encroachment of the distended stomach on the adjacent organs and tissues causes a partial obstruction to their blood supply. That there may be an altered permeability of the mucosa to products in the lumen of the stomach and duodenum and that there may be toxic products entering the circulation from this source or even the peritoneal cavity is very likely, as has been maintained by Hartwell [12] and Brooks [13] and their co-workers. That bacteria may invade the injured gastric wall and play a rôle in the production of toxins is evidenced by the fact that immediately post mortem one of our dogs grossly manifested gas bacillus invasion of the wall of the duodenum. The fact is that prolonged distention of the stomach produces grave morbid changes in the stomach wall which are evident to the unaided eye and which are analogous to the changes reported by numerous workers that occur in the intestine in intestinal obstruction.

A review of our protocols shows that the distention must be present for a considerable period of time before irreversible changes occur, which is well known clinically. If the balloons ruptured or if the distention was released within eighteen to twenty-four hours, the animals survived. Our observations on this point are only suggestive, and because of the variability in the length of life, a large series of animals would have to be used in order to make an accurate statement.

It should be pointed out that in some of our dogs the picture was that of strangulation, in others that of duodenal obstruction with strangulation. Further, it should be kept in mind that with the stomach

12. Hartwell, J. A.; Houget, J. P., and Beckman, F.: An Experimental Study of Intestinal Obstruction, Arch. Int. Med. **13**:701 (May) 1914; Am. J. M. Sc. **143**:357, 1912; J. Exper. Med. **18**:139, 1913.

13. Brooks, B.; Schumacher, H. W., and Wattenburg, J. E.: Ann. Surg. **67**:210, 1918. Copher, G. H., and Brooks, B.: Ann. Surg. **78**:755, 1923.

markedly distended by the method employed in our experiments, some esophageal obstruction is probably present, and hence, the factors operating in the cause of death in esophageal obstruction may have played some rôle in the cause of death in our dogs.

We were caused to study the heart closely in these experiments because of the well known clinical relation of gastric distention and digestive disturbances to angina pectoris, coronary thrombosis, tachycardia and cardiac irregularities. In the clinical texts it is generally stated that acute dilatation of the stomach causes a tachycardia, but that it is slow in onset and related to the toxemia. Vaquez,[14] in discussing tachycardia, stated that distention of the stomach by aerophagia is an occasional cause of this condition. MacKenzie[15] stated that distention of the stomach or colon with gas may lead to cardiac embarrassment. It is well known that tapping the stomach or viscera in the frog causes a slowing of the heart rate. But we have been unable to find any reports on the effect of experimental distention of the stomach on the heart except that of Carlson and Luckhardt[16] in turtles, in which distention of the stomach usually caused acceleration. Our results show that immediately following the distention of the stomach a tachycardia results, except during retching when there occurs the well known vagus slowing and irregularity of cardiac rate. This immediate or early increase in cardiac rate must be due either to reflexes or to a disturbance of the diastolic filling of the heart, or both. We have not sectioned the nerves to ascertain the true mechanism, but in the turtle it does not result after section of the cardiac vagi.[16] After the onset of the toxemia the tachycardia is probably due in part to the effect of toxins. The abolition of the normal sinus arrhythmia is related or due to the tachycardia. The inversion of the T wave and the accentuation of the negative T wave is best explained, we believe, as due to a change in the anatomic axis[17] caused by the distention of the stomach. We explain the accentuation of the Q wave in the same manner. The decrease in the accentuation of the T wave when the dogs were markedly toxic, we interpret as due to a failing heart.[17] The marked changes that occurred in the electrocardiograms of dog 5 (figs. 1, 2 and 3), which manifested possible evidence of abnormal activity of the auricles prior to gastric distention, show that given an abnormal heart to begin with, gastric distention may augment the disturbance. However, since

14. Vaquez, Henri: Diseases of the Heart, trans. by Henry Laidlaw, Philadelphia, W. B. Saunders Company, 1924.

15. Mackenzie, James: Diseases of the Heart, London, Oxford University Press, 1921, p. 360.

16. Carlson, A. J., and Luckhardt, A. B.: Am. J. Physiol. **55**:31, 1921.

17. Katz, L. N.: Physiol. Rev. **8**:447, 1928.

we are not certain that the heart of this dog manifested a slight abnormality prior to distention, it is possible that the distention of the stomach was solely responsible for the postdistention abnormalities.

SUMMARY

1. Continuous distention of the stomach with a volume of water introduced into a balloon—a volume twice that which would be ingested in the form of milk in hunger—caused grave morbid changes to occur in the wall of the stomach and resulted in death in twelve dogs within a period of from twenty-six to ninety hours without a significant fall in blood chlorides and dehydration. The cause of death was toxemia, the mechanism of the production of which is discussed. The changes found at autopsy were not unlike those reported to occur in man in acute dilatation of the stomach.

2. An electrocardiographic study revealed that distention of the stomach causes (*a*) a tachycardia with abolition of the normal sinus arrhythmia manifested by dogs, (*b*) inversion of the T wave or the accentuation of an inverted T wave present in some normal dogs, (*c*) accentuation of the Q wave and (*d*) an exaggeration of preexisting electrocardiographic abnormalities.

NORMAL, ABSENT AND PATHOLOGIC TONSILS IN YOUNG WOMEN

A COMPARISON OF PHYSICAL MEASUREMENTS*

RUBY L. CUNNINGHAM, M.D.
BERKELEY, CALIF.

In an attempt to evaluate the arguments for the removal of tonsils, a study of the histories and physical measurements of young women entering the University of California from 1920 to 1929 was undertaken. The nature of the physical examination required at entrance, the selection of cases studied, the statistical method of handling the data and the comparisons of the histories of those with normal tonsils, of those whose tonsils had been removed and of those with pathologic tonsils have been reported.[1]

The comparison of the physical measurements and of the menstrual experiences of the three groups is here attempted, and should probably carry more conviction than a comparison of histories, since the histories are based on subjective evidence, and are faulty through defective interpretation and memory, while physical measurements are largely objective, and faulty only at the hands of the examiner and recorder.

The measurements available for comparison are: height, deviation of weight from an arbitrarily selected standard for age and height, capacity of the chest, posture, character and number of abnormal vertebral curves, the arches of the feet, complexion, presence and distribution of acne, presence of enlarged cervical glands, character of the thyroid gland, cardiac conditions, heart rate and systolic blood pressure and the condition of the eyes, ears, nasal cavities and teeth. Menstrual experiences are contrasted in: age of onset, length of duration of flow, amount of flow, amount of pain and the presence or absence of irregularity. All measurements are not available for all items for the full ten year period. Capacity of the chest and posture, for instance, were recorded for only the last half of the ten year period.

The statistical material here presented is reliable for comparative purposes when such factors as the accuracy and judgment of the examiner, the excitement of the patient and the methods of measurement

* Submitted for publication, May 27, 1931.

* Aided by a grant from the Research Board of the University of California.

1. Cunningham, R. L.: Normal, Absent and Pathologic Tonsils in Young Women: A Comparison of Histories, Arch. Int. Med. **47**:513 (April) 1931.

similarly affect the three groups contrasted. The records should not form the basis from which standards of physical measurements for young women are derived, unless full allowance is made for the nature and method of the examination.

EXPERIMENTAL DATA

Height, Weight and Capacity of the Chest.—Heights were taken without shoes and recorded in inches and tenths of inches. The mean heights of those with normal tonsils, 63.45 inches, and of those whose tonsils had been removed, 63.64 inches, give a difference of percentages of 0.19 inches, which is greater than three times the standard error of the difference of the means or the amount that can be attributed to chance, and is therefore statistically significant (table 1). The mean height of those with pathologic tonsils was 63.55 inches, which was midway between the mean heights of the other two groups, and not significantly different from either of them.

The greater stature of those whose tonsils had been removed may find explanation in favorable health changes that follow the removal of tonsils. It is, however, possible that concealed factors, such as heredity, past health or standards of living, may be effective in the selection of these groups and may express themselves in certain physical measurements. For instance, tonsillectomy is not as frequent an operation in many foreign countries as it is in the United States. It would therefore be improbable that children of foreign birth or parentage should as frequently have tonsils removed as children of American ancestry. Higher percentages of children who are often ill than of children who are less often ill have tonsils removed.[1] The economic status of the family at times determines whether children shall keep or part with their enlarged tonsils. Other factors than the three mentioned may be present, though not apparent, in the groups of persons selected on the basis of their tonsillar condition and may affect height as well as other physical measurements.

The largest number of weights were taken in light gymnasium suits. During the last three years, students were weighed in bathing suits. A relatively small number were weighed in ordinary clothes without coats, sweaters or shoes. Since judgments as to the state of nutrition are based on a coordination of age, weight and height, it was necessary to select an age, weight and height standard in order to obtain deviations from normal or average weight. When this study was undertaken, the actuarial table of the insurance companies[2] seemed most acceptable and

2. Medico-Actuarial Mortality Investigation, compiled and published by the Association of Life Insurance Medical Directors and the Actuarial Society of America, 1912, vol. 1.

TABLE 1.—*The Means of a Series of Measurements of Physical Characteristics of Young Women with Various Types of Tonsillar Conditions, and the Differences Between These Means and the Measure of the Statistical Reliability of the Differences, That Is, Three Times Their Standard Errors* *

	Means of Physical Characteristics						Differences of the Means			Three Times Standard Error of the Difference of the Means			
	Tonsils Normal		Tonsils Absent		Tonsils Pathologic								
Physical Characteristic	Mean	Standard Deviations	Mean	Standard Deviations	Mean	Standard Deviations	Normal Absent	Normal Pathologic	Absent Pathologic	Normal Absent	Normal Pathologic	Absent Pathologic	Tonsil Group Having the Significant Health Advantage
Mean number of damaged teeth †	9.55	4.9	9.49	4.8	9.35	4.5	0.06	6.20	0.14	0.37	0.41	0.42	63.55
Mean height, inches	63.46	1.4	63.64	1.4	63.55	1.4	0.18‡	0.09	0.09	0.09	0.10	0.11	Absent
Mean weight deviation, pounds	−3.27	14.3	−2.43	15.5	−1.21	15.8	0.84	2.06‡	1.22‡	1.00	1.13	1.16	Pathologic and absent
Mean chest capacity, liters	2.98	0.5	3.01	0.5	3.03	0.5	0.03	0.05‡	0.02	0.04	0.02	0.02	Pathologic
Mean systolic blood pressure	116.06	11.7	115.67	12.2	116.62	12.2	0.39	0.56	0.95‡	0.79	0.87	0.61	?
Mean pulse rate	89.76	13.6	88.82	14.2	89.71	14.3	0.94‡	0.05	0.89	0.91	0.99	1.02	Absent
Mean climacteric period, years	13.28	1.27	13.17	1.25	13.29	1.28	0.11‡	0.01	0.12‡	0.08	0.09	0.09	?
Mean duration of menses, days	4.81	1.16	4.88	1.15	4.81	1.14	0.07	0.00	0.07	0.07	0.08	0.08	

* The original figures from which the percentages, means and standard deviations have been calculated are on file and available for consultation. This study includes 4,185 women with normal tonsils, 4,134 women whose tonsils had been removed, and 2,836 women with pathologic tonsils.

† In students with no teeth absent.

‡ Statistically significant difference.

was selected for this purpose. The weights on which actuarial tables are based were taken without shoes, but in light clothes, and must, therefore, be a few pounds heavier than weights taken for this study.

Those with normal tonsils were most underweight (table 1); those with pathologic tonsils least underweight. The differences in means of weight deviations of the groups with normal tonsils and pathologic tonsils and of the groups without tonsils and with pathologic tonsils are statistically significant. If these nutritional variations are credited to the condition of the tonsils, there is no argument in this field for the removal of pathologic tonsils. Concealed factors may, however, be effective here, as well as in mean height determinations.

For the determination of the capacity of the chest, the spirometer was used and the greatest amount of air expired, measured in liters. Since the use of the spirometer was new to many subjects, they were often given two or more trials, and the highest figure registered was accepted for record (table 1). There was a significant difference between the mean capacity of the chest of those with normal and of those with pathologic tonsils. The latter group had the greater mean capacity (table 1).

Posture, Vertebral Curves and Feet.—Estimates of posture in terms of *A, B, C, D* and *E* were recorded for all entering students who were required to register in physical education classes [3] (table 2). The numbers in the superior, *A*, rating, and in the poorest, or *E*, rating, were so small as to be almost negligible. The groups of those whose tonsils had been removed and of those with pathologic tonsils had practically the same incidence in the *B, C* and *D* ratings. The significance of the higher percentages of those with normal tonsils in the *C* rating was minimized or nullified by the lower percentage of persons of this group in both the better, or *B*, rating, and the less favorable, or *D*, rating. There seems, therefore, to be no appreciable influence of tonsillar condition on posture.

Where vertebral curves assumed unusual degrees, they were recorded as instances of kyphosis, lordosis and scoliosis (table 2). For 9,951 students for whom such criticisms of the vertebral column were made, the incidence in the three groups differed by less than 2 per cent. Such differences in percentages are too small to have statistical significance. Tonsillar condition does not seem to relate itself to any type of exaggerated vertebral curvature.

The character of the arches of the feet was carefully observed and recorded, although not in the same terms, for the ten year period. For a number of years, the designations of high, medium and flat were used.

3. Klein, Armin: Posture Clinics, United States Dept. Labor, Children's Bureau, 1926, p. 164.

TABLE 2.—*The Percentages of Incidence of Physical Characteristics in Young Women with Various Tonsillar Conditions, with Differences Between These Percentages and the Measure of the Statistical Reliability of the Differences, That Is, Three Times Their Standard Errors*

Physical Characteristics	Percentage Incidence of Physical Characteristics			Difference in the Percentage Incidences			Three Times Standard Error of the Difference of Percentages			Tonsil Group Having the Significant Health Advantage
	Tonsils Normal	Tonsils Absent	Tonsils Pathologic	Normal Absent	Normal Pathologic	Absent Pathologic	Normal Absent	Normal Pathologic	Absent Pathologic	
Blond skin	19.09	17.73	20.59	1.36	1.50	2.86	2.58	2.94	2.91	
Demiblond skin	48.44	50.44	48.56	2.00	0.12	1.88	3.33	2.69	3.68	
Brunette skin	32.46	31.83	30.85	0.63	1.61	0.98	3.12	3.42	3.42	
Acne of face	11.23	8.80	10.60	2.43*	0.63	1.80	2.01	2.31	2.20	Absent
Acne of chest	13.50	10.30	11.64	3.20*	1.90	1.34	2.16	2.43	2.30	Absent
Acne of back	20.83	16.31	18.50	4.53*	2.33	2.19	2.59	2.71	2.81	Absent
Cervical glands enlarged	21.61	22.85	20.79	1.24	0.82	2.06	2.76	3.00	3.04	
Thyroid normal	74.33	74.70	71.15	0.37	3.18*	3.58*	2.88	2.97	2.98	Normal and absent
Thyroid adolescent	23.40	21.82	25.82	1.58	2.42	4.00*	2.76	3.15	3.14	Absent
Thyroid with adenoma	2.26	3.41	2.94	1.15*	0.68	0.47	1.08	3.72	1.27	Normal
Posture A	1.40	1.27	1.31	0.13	0.09	0.04	0.90	1.59	1.57	
Posture B	23.99	28.46	27.61	4.47*	3.62	0.85	3.36	6.24	6.22	Normal
Posture C	62.43	53.58	55.75	8.85*	6.68	2.17	3.75	6.96	6.91	
Posture D	11.53	16.09	14.63	4.56*	3.10	1.46	2.58	4.89	4.93	Normal
Posture E	0.65	0.59	0.70	0.06	0.05	0.11	0.60	1.17	0.54	
Vertebral kyphosis	15.05	15.89	16.68	0.84	1.63	0.79	2.67	5.87	5.83	
Vertebral lordosis	8.73	9.94	9.36	1.21	0.63	0.58	2.13	4.56	4.57	
Vertebral scoliosis	20.76	18.37	19.90	2.39	0.86	1.53	2.94	6.30	6.23	
Long arch of foot high	14.55	19.38	16.73	4.83*	2.18	2.65	2.58	2.79	2.93	Absent
Long arch of foot medium	75.30	75.78	77.78	0.48	2.48	2.00	2.94	3.21	3.23	
Long arch of foot low or flat	10.14	4.83	5.52	5.31*	4.62*	0.69	1.79	1.98	1.70	Absent and pathologic
Anterior arch of foot present	77.92	75.27	75.07	2.65	2.85	0.20	2.91	3.24	3.31	
Sight of both eyes 20/20	56.46	55.52	59.71	0.94	3.25	4.19*	3.36	3.69	3.60	Pathologic
Eyes farsighted	23.95	24.72	21.07	0.77	2.88	3.65*	2.91	3.12	3.02	Pathologic
Eyes nearsighted	19.26	19.99	19.38	0.73	0.12	0.61	2.67	2.94	2.99	
Eyes astigmatic	20.72	17.57	14.91	3.15*	5.81*	2.66	2.64	2.82	2.76	Pathologic and absent
Ears normal	93.36	93.39	91.80	0.03	1.56	1.59	1.65	1.92	1.94	
Nose normal	74.68	70.41	61.84	4.27*	12.84*	8.57*	2.94	3.39	3.47	Normal and absent
Nasal spur present	7.35	7.36	9.15	0.01	1.80	1.79	1.71	2.01	2.03	
Nasal septum deviated	16.87	20.12	27.02	3.25*	10.15*	6.90*	2.55	3.03	3.13	Normal and absent
Chronic rhinitis	2.78	3.04	4.11	0.26	1.33	1.07	1.11	1.34	1.37	
All teeth present	71.30	73.55	70.84	2.25	0.46	2.71	2.91	3.30	3.28	
No teeth absent and no fillings	3.95	3.22	4.58	0.73	0.63	1.36	1.50	1.74	1.75	

* Statistically significant difference.

Recently, the four grades of high, medium, low and flat have been recorded. For purposes of simplicity, the three groups, high, medium and low, which includes flat, have been interpreted from other designations, and thus recorded (table 2).

It would seem that normal tonsils and poor feet go hand in hand, since the group of those with normal tonsils had fewer high arches and considerably more low and flat longitudinal arches than either of the other two groups. The anterior arches were present in from 75 per cent to 78 per cent of subjects in all of the groups, and differences in percentages between any two are without significance.

The longitudinal arches of the feet and the condition of the tonsils are interdependent or dependent on some common factor. The largest number of persons with poor feet were found among those with normal tonsils.

Skin, Thyroid and Lymph Glands.—Since both the skin and the superficial layers of tonsillar tissue are of the same embryologic origin, it seems possible that a characteristic or pathologic condition of the former might be reflected in the latter. Blonds, demiblonds, demibrunettes and brunettes included approximately the same percentages of persons with normal tonsils, tonsils that had been removed and pathologic tonsils. Apparently, complexion does not predispose to pathologic change or normality of the tonsils. Acne offers more affirmative evidence of a relation to tonsillar condition than does complexion. Those whose tonsils had been removed had clearer faces, chests and backs than did either of the other two groups (table 2). If it were not for the fact that those with pathologic tonsils had clearer skins than those with normal tonsils, and almost as clear skins as those whose tonsils had been removed, there would be an argument for the removal of tonsils, especially in cases in which acne is persistent or disfiguring.

The condition of the tonsils had little effect on the presence or absence of palpable cervical glands, since differences in the percentages of their occurrence in the three groups were within the limits of error due to chance selection (table 2).

A definite relationship seems to exist between the condition of the tonsils and that of the thyroid gland. About the same percentages of those with normal tonsils and of those whose tonsils had been removed had a normal thyroid gland, while fewer of those with pathologic tonsils had a normal gland (table 2). Those with pathologic tonsils had a significantly higher number of adolescent enlargements of the thyroid than those with normal tonsils or those whose tonsils had been removed, while those without tonsils had the highest percentage of adenomas of the thyroid of the three groups.

Cardiac Conditions and Blood Pressure.—Evidence of cardiac disease as determined by physical examinations was discussed in the article already presented,[1] since such evidence is related so intimately to the history of cardiac disease and rheumatism. Although there were some suggestive relationships between the tonsillar condition and pathologic change in the heart, none were sufficiently clear to warrant definite conclusions.

The curves of the pulse rates of those with normal tonsils, of those without tonsils and of those with pathologic tonsils were very similar. The mean pulse rate of those whose tonsils had been removed was significantly, though slightly, less than the means of either those with normal tonsils or those with pathologic tonsils (table 1). Since all of the mean pulse rates in this study were considerably above the accepted average, or normal, the group of those whose tonsils had been removed most nearly approached normal.

The mean blood pressure of the group of those whose tonsils had been removed was lower than the mean of either of the other two groups (table 1); the difference between the means of those with normal tonsils and of those without tonsils was small enough to credit to the chances of simple sorting, while the difference between the means of the blood pressures of those without tonsils and of those with pathologic tonsils was great enough to deserve an explanation. As yet, there is no accepted optimum of blood pressure for various age groups, so it is difficult to decide whether those with no tonsils and a mean blood pressure of 115.67 mm. of mercury or those with pathologic tonsils and a mean blood pressure of 116.62 mm. are most fortunate.

The effect of the condition of the tonsils on the heart and the circulation was slight, and was difficult to evaluate and to interpret.

Eyes, Ears and Nose.—The eyes of students entering the University of California were examined by an oculist. When the sight was recorded as 20/20 for both eyes and no notes made as to existing abnormalities, the eyes were considered and are here recorded as normal (table 2). A note was made in the history of whether or not glasses were worn. The group with pathologic tonsils had the highest percentage of normal sight, 59.7 per cent; 30.6 per cent wore glasses. Those with normal tonsils had the next highest percentage of normal sight, 56.5 per cent; 33.4 per cent of them wore glasses. Those whose tonsils had been removed had the poorest sight, only 55.5 per cent having normal vision; 41.5 per cent of this group wore glasses. Those with pathologic tonsils seemed to fare better than did members of the other two tonsillar groups in that they had considerably less astigmatism. The fact that those with pathologic tonsils had the best sight offers a temptation to hunt for an explanation in the fact that tonsillar groups are in themselves selective

groups. Children who have their tonsils removed come in large proportion from native born stock, from health conscious families and from families of better material circumstances rather than from the poorer classes; they are from urban rather than from rural communities, and they have experienced more illness than have either those whose tonsils are normal or those whose tonsils are pathologic. It seems possible that the sight of the individuals in the three groups was more affected by the factors that determine the selection of the groups than by the condition of the tonsils.

The examination of the ears was somewhat unsatisfactory on account of the number of external ear canals occluded by wax. The percentages of ears that were clear and thought to be normal varied between 91.8 per cent and 93.4 per cent, and the difference in percentages in the three groups were without significance (table 2).

There seems to be a positive relationship between the nasal and the tonsillar condition. Normal tonsils were associated with the highest incidence of normal nasal cavities (table 2). Persons without tonsils, in turn, fared better in nasal conditions than did those with pathologic tonsils in whom the highest percentages of deviated septums, spurs and evidence of chronic rhinitis were found. The differences in percentages are all suggestive, and a number have statistical significance.

Teeth.—Dental examinations of students entering the university were made by dentists, and careful records were kept of all filled or carious teeth, of absent teeth and of dental appliances. Since many of the students examined had not yet erupted the third molars, a separate record of these four possible teeth was made, and they are not included in the table presented. Fillings, crowns or cavities in the third molars that were present are not included in counts of damaged teeth (tables 1 and 2).

The number of teeth filled, crowned or with cavities was counted, and listed for all students, regardless of whether teeth were absent or not. Nowhere did differences in the three groups appear. The data of greatest reliability, especially when combined with those on the number of missing teeth, seemed to be those concerning persons with no teeth absent, and are here presented (table 1).

The mean number of damaged teeth in the three groups differed by amounts that are within the variations of chance. No reciprocal relationship between the tonsillar and the dental condition was apparent.

Menstrual Characteristics.—Menstrual experiences, such as age of onset, duration, amount of irregularity, amount of flow and degree of pain, as judged by data gathered from histories taken at the time of the entrance of the students to the university, were remarkably similar in the three groups selected on the basis of the tonsillar condition (table 1).

The only difference in percentages that has value is in the age of onset. Those whose tonsils had been removed menstruated first at 13.17 years, whereas those who had normal and pathologic tonsils menstruated first at 13.28 and 13.29 years, respectively.

Here, as in the case of determinations of the blood pressure, the lack of an established optimum value makes it difficult to determine where health advantage is to be placed, with the earlier establishment of menstruation of those whose tonsils had been removed or with the later establishment of menstruation of the other two groups.

SUMMARY

1. Reference is made to my published paper presenting the relationships existing between the histories of disease, operation and cardiac condition of persons with normal tonsils, persons whose tonsils have been removed and persons with pathologic tonsils. In that paper the source of the material and its method of organization and presentation is described and the related literature reviewed.

2. The physical measurements of height, weight deviation from an arbitrary standard, capacity of the chest, posture, character and number of abnormal vertebral curves, arches of the feet, complexion, presence and distribution of acne, presence of enlarged cervical glands, character of the thyroid, cardiac conditions, heart rate and systolic blood pressure, condition of the eyes, ears and nasal cavities, condition of the teeth and menstrual experiences of young women with normal, absent and pathologic tonsils are here contrasted.

CONCLUSIONS

The outstanding relationships between physical measurements and tonsillar conditions brought out by this study are:

1. The condition of the tonsils, whether normal, absent or pathologic, has little effect on the physical condition of young women of college age, from 15 to 35 years.

2. No significant relationship exists between the complexion and the tonsillar condition or between the tonsillar condition and the percentage of palpable cervical glands, the posture, the exaggeration of vertebral curves and the ear and dental conditions.

3. No significant relationship exists between the tonsillar and the menstrual conditions as judged by the mean duration of menstruation in days, the amount of pain, the amount of flow and the amount of irregularity.

4. Those who have had their tonsils removed have less acne than those with pathologic tonsils, who in turn have less acne than those with normal tonsils.

5. A larger number of those with pathologic tonsils than either of the other two groups have thyroid glands with adolescent enlargements.

6. Those with normal tonsils have poor feet, as judged by the percentages of those with low and flat longitudinal arches.

7. Those with pathologic tonsils have better vision and fewer ocular defects than those with normal tonsils or those whose tonsils have been removed.

8. The most perfect nasal structures are found in the group with normal tonsils. Those without tonsils have better nasal cavities than those with pathologic tonsils, in which group are found the largest number of deviated septums.

9. Those whose tonsils have been removed attain a mean height of from one tenth to one fifth of an inch greater than those who have kept them.

10. The mean weight of those who have pathologic tonsils is greater than that of those without tonsils, whose weight in turn is greater than that of those with normal tonsils.

It is suggested that these groups are somewhat determined by such factors as heredity, place of residence, past health history, standards of living and attitude toward medical care, and that these factors are effective and are to some extent responsible for the differences in physical measurements found in the three groups selected on the basis of their tonsillar condition.

COMMENT [4]

The condition of the tonsils is of minor importance in influence on the health history and the determination of physical measurements of young women. Such influence is tangled with that of factors determining whether pathologic tonsils shall be removed or not, and is therefore difficult to evaluate.

The contention that normal tonsils are an aid in resisting disease is not strongly defended by contrasting the histories of disease of those with normal and those with pathologic tonsils. The argument that the removal of tonsils closes a portal of entry for infectious and respiratory diseases is not sustained by a comparative study of the histories of those who have had their tonsils removed and of those whose tonsils are present. The effect of the tonsils as a focus of infection does not find much support when histories and physical measurements of those with pathologic tonsils are contrasted with either those with normal or those with absent tonsils.

---

4. The comment is based on the comparison of histories (footnote 1) as well as on the comparison of physical measurements.

The effect of normal tonsils in augmenting growth or of pathologic tonsils in retarding development is not apparent in this study. The effect of the tonsils on the glands of internal secretion is suggested in the thyroid findings, but is not evident in comparative menstrual experiences or in the results of growth. The theory that the tonsillar condition is influenced by diet and reflects nutritional conditions, as may teeth, stature and weight, is not greatly aided by the findings of this investigation.

This study does not emphasize the arguments for the removal of tonsils other than for the cure of a local throat condition. Similar studies at younger and at older age levels should be undertaken to evaluate further the arguments for the removal of tonsils.

PSITTACOSIS

REPORT OF FIVE CASES *

MEYER A. RABINOWITZ, M.D.
AND
SEYMOUR H. LIVINGSTON, M.D.
BROOKLYN

In this communication is presented a household outbreak of five cases of psittacosis running a characteristic course, with definite pathologic as well as biologic evidence substantiating the diagnosis. These followed the importation of a group of love birds or parrakeets from Havana.

Parrakeet is the name given to certain subgroups of the family Psitticae or parrots.[1] It includes especially the parrots of relatively small size and slender form with a long graduated tail; e. g., the subfamilies of Palaeonithinae and Platycercinae of Asia, Australia and Polynesia, and the Cornurinae of South and Central America. The latter is still to be found in the southern part of the United States and is sometimes spoken of as the Carolina parrakeet.

According to Roubakine,[2] the disease psittacosis in man is caused, in the vast majority of cases, by the green parrot of the species Chrysotis amazonicus. However, he mentioned an epidemic of the disease that occurred in Zulpich, in the Rhineland, in 1909, which was due entirely to the Australian parrakeet. In the widespread epidemic of one year ago, mention was made by Anderson [3] of cases in which the disease was contracted from canaries. Armstrong [4] noted parrots, parrakeets, love birds and canaries as sources of infection. The experimental work of Rivers, Berry and Rhoades,[5] in which they succeeded in inoculating parrots, mice, rabbits, guinea-pigs and monkeys with the disease, would seem to indicate that any of these species might be a

* Submitted for publication, June 29, 1931.

* From the medical service of Meyer A. Rabinowitz, Jewish Hospital of Brooklyn, N. Y.

1. Salvadori, A. T.: Catalogue of Parrots in the Collection of the British Museum, London, Longmans & Company, 1891.

2. Roubakine, A.: Monthly Epidemiological Report of the League of Nations **9**:141 (April) 1930.

3. Anderson, G. W.: New England J. Med. **204**:67 (Jan. 8) 1931.

4. Armstrong, C.: Pub. Health Rep. **45**:2013 (Aug. 29) 1930.

5. Rivers, T. M.; Berry, G. P., and Rhoades, C. P.: Psittacosis: Observations Concerning Experimental Disease in Parrots, Mice, Rabbits, Guinea-Pigs and Monkeys, J. A. M. A. **95**:579 (Aug. 23) 1930.

potential carrier of infection. In addition to the susceptible animals mentioned, Ward and Gallagher [6] included the pigeon and fowl.

The parrakeets concerned in this report were purchased in Havana, Cuba, by one of the patients, Mrs. B., Jr., who gave them to the butcher on board ship to take care of during the return trip to New York City. This is a general practice among tourists bringing pets back to this country. On arrival at New York two of the birds were delivered to a neighbor. Of these two, one was found dead when received, while the other died shortly after reaching the neighbor's home. Neither of these birds gave rise to any cases of psittacosis. Of the four remaining birds, two were given to Mr. B., Sr. (case 1), father-in-law of Mrs. B., Jr. On the first night, Mrs. B., Jr.'s, male bird and Mr. B., Sr.'s, female bird escaped from their cages and were never located. The remaining birds were remated under the care of Mr. B., Sr.

On January 13, nine days after the birds came into his house, Mr. B., Sr., who was very fond of them and himself took care of them, became ill with a very severe pneumonic infection, and died after five days of illness. He was buried on January 19, and, as is the custom in an orthodox Jewish household, the family gathered at the home of the deceased to observe for one week a period of mourning. During this week an intestinal disturbance developed in one of the two remaining birds, and it soon died with a "protruding rectum." All the mourners were exposed to both the sick and the "well" bird. On January 28, nine days after the family group gathered, Mrs. H., sister of Mr. B., Sr., took ill. On February 3, Mrs. G., daughter of Mr. B., Sr., on February 5, Mrs. S., another daughter of Mr. B., Sr., and on February 8, Mrs. B., Jr., the importer of the birds, fell sick.

Although the one remaining bird was apparently still healthy, Dr. G. P. Berry of the Rockefeller Institute was able to demonstrate the psittacosis virus in its organs.

For obvious reasons the case reports are markedly abbreviated.

REPORT OF CASES

CASE 1.—Mr. B. Sr., aged 65, took ill on January 13, complaining of chills, fever and headache. His temperature rose rapidly to 103.8 F., and on the following day he showed diffuse signs of bronchopneumonia in both lungs. Death occurred on the fifth day of illness.

Owing to the prevalence at that time of a local "influenzal bronchopneumonia" epidemic, and the fact that the patient had previously been suffering from chronic bronchitis, emphysema, severe cardiac failure and hypertrophied prostate, his illness and demise created no suspicion until the other members of the family began to come down

6. Ward, A. R., and Gallagher, B. A.: Diseases of Domesticated Birds, New York, The Macmillan Company, 1920.

with pneumonic disease. At this time a common etiologic factor was looked for, and at once suspected as psittacosis infection because of the history of the parrakeets.

Case 2.—Mrs. H., aged 51, obese, on January 28 began complaining of chilly sensations, fever and malaise, and later of palpitations. She was admitted to the Jewish Hospital (as were the subsequent patients) on February 5, extremely ill, prostrated, toxic and cyanotic, with a distressing hacking cough, but absolutely no expectoration. There were signs of extensive patchy pneumonic involvement of both lungs. The temperature ran an extremely high, flat, plateau-like course. The respirations were very rapid. A typhoidal state soon developed, with low muttering delirium, distressing abdominal distention and persistent, extremely foul loose, watery diarrhea. Examination of the stool for typhoid bacilli proved negative. The pulse became irregular, and death occurred on the seventeenth day of illness. Examination by Dr. G. P. Berry of the blood and sputum of the patient taken on the thirteenth day of the illness failed to reveal the presence of the psittacosis virus. However, it was successfully demonstrated in the liver, lungs and spleen removed at autopsy.[7]

Important anatomic data were: lobular pneumonia; thrombosis of the pulmonary artery, pulmonary veins, iliac vein and splenic vein; gastro-enteritis, and multiple hemorrhages of the spinal cord with chromatolysis, satellitosis and fat replacement of the anterior horn cells.

Case 3.—Mrs. G., aged 40, became ill on February 4, complaining of pain in the back below both scapulae and malaise. Her temperature was 101 F. During the following two days she experienced repeated chilly sensations, and her temperature rose to 103.8 F. On February 7 she was admitted to the Jewish Hospital, extremely ill, toxic, prostrated and complaining of severe pain in the left side of the chest, anteriorly and posteriorly, and of a hacking unproductive cough. Examination of the chest gave negative results. Severe headache, marked apathy and listlessness were present throughout. On the seventh day of the illness, numerous extremely fine crepitant râles were heard in the right side of the chest, and roentgen examination confirmed the impression of incomplete consolidation of the upper lobe of the right lung. The temperature gradually fell to normal on the twelfth day of the illness. The hacking cough persisted with very scant mucoid expectoration. On the seventh day the patient had a severe diarrhea consisting of five loose watery stools, not foul in nature. After two days of normal temperature, the patient went into collapse from a pulmonary embolus. With prompt and continuous use of the oxygen tent, she gradually rallied. The rally was followed by evidence of thrombosis of the left saphenous vein. Sputum and blood taken on the seventh day of the illness for examination for the psittacosis virus proved negative.

Case 4.—Mrs. S., housewife, aged 37, became ill on February 5, complaining of chilliness, feverishness and weakness. On the following day, her temperature was 102 F. On February 7, a severe throbbing right-sided headache developed. The patient was moderately prostrated and slightly cyanotic. The lungs were apparently clear.

There was no cough. The tongue was grayish brown with clear edges. The patient's mental condition was good, but the headache was extremely distressing.

7. A detailed report of the autopsy observations is given by Polayes, S. H., and Lederer, M.: Psittacosis; Postmortem Examination of a Case, Including Studies of the Spinal Cord, Arch. Int. Med. **49**:253 (Feb.) 1932.

On February 11, fine crepitant râles were heard at the base of the right lung posteriorly, and on the following day a roentgenogram revealed an area of dense, sharply demarcated consolidation just above the middle of the right pulmonic field peripherally. On February 18, the left lung showed signs which soon involved the entire lung. The temperature curve showed two distinct cycles. On March 5, pain and tenderness developed in the left calf, which were interpreted as evidence of deep venous thrombosis. Specimens of the sputum and blood taken on the sixth day of the illness proved negative for psittacosis virus.

CASE 5.—Mrs. B., Jr., aged 32, was admitted to the Jewish Hospital on February 8 following an illness of only one day. This began with chilly sensations, high fever and an exacerbation of a preexisting cough. She was moderately prostrated, not markedly cyanotic, but had a harsh cough with occasional blood-tinged expectoration. The signs in the chest showed great tendency to vary from day to day, most râles being extremely fine. A roentgenogram of the chest on February 12 revealed an area of dense consolidation in the upper field of the left lung. The temperature showed two distinct cycles, falling to normal by the twenty-first day of illness. Headache was not a prominent feature in this case, and there was neither diarrhea nor clinical evidence of thrombosis. The cough was especially distressing. A smear of the sputum showed scanty cytology, consisting chiefly of lymphocytes with an occasional polymorphonuclear neutrophil, a few large epithelial cells, a moderate number of large cells with pale nuclei and pale pink protoplasm and a few red blood cells. Examination of the sputum taken on the third day of illness definitely demonstrated the presence of the psittacosis virus. The virus could not be found in the patient's blood taken at the same time.

HISTORICAL REVIEW

The first description of psittacosis to be found in the literature is that of Ritter [8] who described an epidemic that occurred in Switzerland in 1879. This consisted of seven cases of a severe atypical pneumonia or "pneumo-typhus," with three deaths. The epidemic was attributed by Ritter to a shipment of parrots recently received from Hamburg. Since that time numerous reports of small epidemics of a similar nature have appeared, but it was not until the large Paris epidemic of 1892-1895 that Morange gave the disease the name psittacosis from the Greek ψιττακός meaning parrot. This Paris epidemic consisted of seventy-eight cases with twenty-four deaths, and was caused by the importation of five hundred birds from the Argentine.

The first report of psittacosis in this country was in 1904, when Vickery and Richardson [9] reported three probable cases. Scott [10] in 1906 recorded three cases. The next report was in 1917 by McClintock [11] who described thirteen cases in Wilkes-Barre, Pa., with only one death. In 1929, the report of a single case with recovery was published by Sailer [12] in Philadelphia.

8. Ritter, J.: Deutsches Arch. f. klin. Med. **25**:53, 1879.
9. Vickery, H. F., and Richardson, O.: Tr. Am. Physiol. Soc. **19**:364, 1904.
10. Scott, H. N.: Tr. New Hampshire M. Soc., 1906, p. 168.
11. McClintock, A. T.: Arch. A. T. McClintock Mem. Found. **1**:1, 1925.
12. Sailer, J.: M. Clin. North America **12**:1095 (Jan.) 1925.

In 1930, there was the great pandemic that started in the city of Cordoba, Argentine,[13] and involved in its spread continental Europe, England,[14] the United States,[15] Canada and Hawaii. Approximately five hundred cases were reported within a period of one year.[16] In this country, Armstrong [4] recorded the occurrence of one hundred and sixty-nine cases from Nov. 23, 1929 to May 7, 1930. Since this time there have been reports of many cases from numerous sources and in all parts of the country. These total approximately sixty-five cases.[17]

CLINICAL FEATURES

The disease was insidious in its onset, beginning with chilly sensations, malaise and fever. However, in one case there was a sudden onset, with an abrupt rise of temperature to 104 F. Cough was usually present, but was not prominent except in one case. A characteristic feature was the extremely thick, mucoid expectoration, occasionally blood-tinged. This tenacious sputum is in keeping with the microscopic appearance of the lung post mortem, i. e., the prominent network of interlacing fibers of fibrin which sometimes completely fill the alveoli.

A diagnosis of grip or influenza is often made. In our cases we were impressed by the absence of the extremely hyperemic oropharynx seen in "influenza."

Pulmonary signs may not appear until the disease is well advanced. In two cases there were two distinct cycles of the disease, the second appearing with the involvement of a new pulmonary area. An important finding is the persistent, very fine crepitant râles in the involved area. The absence of any evidence of pleuritic involvement, clinical or pathologic, in the presence of extensive pulmonary pathologic involvement, is in keeping with the findings of MacLachlan, Permar and Rogers.[18]

13. Barros, E.: Rev. Asoc. méd. argent. **43**:17 (Jan.-April) 1930; abstr., Lancet **1**:472 (March 1) 1930.

14. Thomson, A. P., and Hillier, W. T.: Lancet **1**:396 (Feb. 22) 1930.

15. Anderson (footnote 3). Armstrong (footnote 4). Peterson, E.; Spalding, O. B., and Wildman: Psittacosis: A Clinical and Roentgenologic Study of Seven Cases with Postmortem Observations in One Case, J. A. M. A. **95**:17 (July 19) 1930. Bortz, E. L., and Green, B.: Psittasosis, J. A. M. A. **95**:400 (Aug. 9) 1930. Rivers, T. M.; Benjamin, B., and Berry, G. P.: Psittacosis; Report of a Case, J. A. M. A. **95**:577 (Aug. 23) 1930. Wellman, H. E.: New England J. Med. **203**:421 (Aug. 28) 1930. Sandoer and Coburn: J. Kansas M. Soc. **31**:280 (Aug.) 1930. Kahn, T. F., Jr.: Yale J. Biol. & Med. **2**:417 (July) 1930. Haines, H. G.: Psittacosis; Study of Three Cases, J. A. M. A. **94**:1821 (June 7) 1930. Reisman, D., and Davidson, H. S.: M. Clin. North America **14**:815 (Jan.) 1931.

16. Wellman, H. E.: New England J. Med. **203**:421 (Aug. 28) 1930.

17. Gorham, L. W.; Calder, F. G., and Vedder, J. D.: Psittacosis; Report of Five Cases, J. A. M. A. **94**:1816 (June 7) 1930.

18. MacLachlan, W. W. G.; Permar, H. H., and Rogers, C. A.: Ann. Int. Med. **4**:260 (Sept.) 1930.

One prominent feature of the disease was the tendency to thrombosis. There was no change in the bleeding or coagulation time in any case. Thrombi were found post mortem in the pulmonary vessels, right iliac vein and splenic vein in case 2. In case 3, a pulmonary embolus was the first indication of an extensive thrombosis of the veins of the left leg. In case 4, there was evidence of deep peripheral venous thrombosis. It would be well to bear this feature of the disease in mind, both from a therapeutic and a prognostic point of view. Mention of thrombophlebitis as a common complication was made by Armstrong [4] in his survey of the epidemic of 1930 in the United States. We also noted a report of two deaths due to pulmonary embolus during an outbreak of psittacosis among the employees of a department store, recorded by Badger.[19]

Headache was extremely prominent in two cases, but less marked in two others. It is likely that this has a definite pathologic basis in the marked congestion of the meninges. The spleen was palpated in only one case, and a transient roseolar eruption noted in one. The tongue showed a grayish-brown coat with clean edges in all cases.

The temperature showed wide, daily fluctuation in most cases, but in one fatal case (case 2) assumed the plateau-like fastigium. The pulse and respirations were in no way distinctive. The leukocyte count was characteristically but slightly increased, ranging between 9,000 and 13,000, with a percentage increase of the polymorphonuclear cells. In all cases eosinophilic leukocytes were found on at least one occasion during the active phase.

The ages of our patients varied from 32 to 65. The two fatalities occurred in the older persons, who also happened to be the first to be affected. The diminished resistance of the elderly patient to this disease as compared to the more youthful one has been pointed out by Horder and Gow.[20] In the older person, the disease runs an extremely rapid, fatal course, while in the younger patient it may be relatively innocuous and mild.

The incubation period of the disease is rather clear in two of our cases. In cases 1 and 2 a definite period of nine days between the first exposure and the appearance of symptoms is demonstrable.

SUMMARY

1. Five cases of psittacosis occurring in one family are presented, with autopsy observations in one.

2. The disease in these cases is distinctly attributable to exposure to infected love birds or parrakeets brought to this country from Havana.

19. Badger, L. F.: Pub. Health Rep. **45**:1403 (Feb. 1) 1930.
20. Horder, T., and Gow, A. E.: Lancet **1**:237 (Feb. 1) 1930.

Cuba, by returning tourists. This is of extreme epidemiologic and diagnostic importance.

3. Biologic evidence of the identity of the disease was possible in this epidemic, the virus of psittacosis being clearly demonstrated (*a*) in the sputum of one of the patients (case 5), (*b*) in the liver, lung and spleen of another (case 2) and (*c*) in the liver and spleen of the only bird available for examination. That this bird was apparently healthy is of great epidemiologic importance.

4. The characteristic clinical points of diagnostic importance are: (*a*) History of exposure to a diseased bird. (*b*) Incubation period of approximately nine days. (*c*) Marked headache. (*d*) Toxemia which may be decidedly out of proportion to the physical findings in the chest. (*e*) Slight cough with extremely scanty, thick, tenacious expectoration which may or may not be blood-tinged. Further observation is necessary to determine whether microscopic study of the sputum (case 5) is characteristic of the disease. (*f*) An extremely fine type of crepitant râle. (*g*) Roentgen evidence of dense consolidation of part of a lobe of the lung almost from the very onset of symptoms. (*h*) No pleuritic involvement in the face of extensive pulmonary pathologic involvement. (*i*) Moderate or no leukocytosis in the presence of severe pneumonic infection. (*j*) Tendency to venous thrombosis.

CHOREA GRAVIDARUM

A STATISTICAL STUDY OF 951 COLLECTED CASES, 846 FROM THE LITERATURE AND 105 PREVIOUSLY UNREPORTED*

PRENTISS WILLSON, M.D.
AND
ALEC A. PREECE, M.D.
WASHINGTON, D. C.

In the summer of 1925 the attention of one of us (Dr. Willson) was directed to the complication of pregnancy with chorea by the opportunity to study a case and to treat the patient in his private practice. The patient recovered, but was so desperately ill and presented such a terrifying picture at the height of the disease that she aroused the greatest interest in all who saw her. A cursory examination of the literature undertaken at the time she was under treatment made it obvious that chorea gravidarum was a serious and very rare condition, with an estimated mortality of approximately from 25 to 33.33 per cent, and that there was absolutely no unanimity of opinion as to its true character, and hence, naturally, no accepted therapeusis, particularly with reference to the question of the necessity for interrupting pregnancy. These findings have led us to avail ourselves of the opportunity afforded by the report of this case to present a complete and comprehensive study of the whole subject. Obviously, in order to be of value, such a survey of any medical condition must present a composite picture of the disease, based on many observations, clearly demonstrating all its possible variations in course, duration, severity, complications, etc. In no other way are sound generalizations on the subjects of etiology, pathology, prognosis and treatment possible. When the disease under investigation is one as rarely seen as chorea gravidarum, the opportunity to observe which, even in the material of a large clinic, may not occur for years, the only feasible approach to the problem would seem to lie in collecting the largest possible number of cases from the literature and any other available sources in order that their data may be subjected to critical analysis. With this end in view, a thorough search of the literature to Sept. 30, 1930, was undertaken, and, in addition, 530 questionnaires were sent to the members of several American obstetrical societies with the result that this paper is based on the analysis of the more or less detailed reports of 1 personal case, of 846 choreic pregnancies, occurring in 711 patients, reported in the literature, and of 104 choreic pregnancies,

* Submitted for publication, June 18, 1931.

* The cases from the literature include those published to Sept. 30, 1930.

occurring in 85 patients, reported by those replying to the questionnaire, thus assembling for study a total of 951 choreic pregnancies in 797 persons. This material has been abstracted in tabular form in table 1 under the following captions: Age, social status (married or single), parity, previous history of chorea, previous history of rheumatism, evidence of cardiac disease, month of pregnancy in which chorea had its onset, duration of attack, fate of the pregnancy, result to mother, result to child and comment (autopsy observations, notes on treatment, condition of urine, blood pressure, blood picture, etc.).

Since the main purpose of this communication is to throw as much light as possible on the matter of the true character of chorea gravidarum, it has seemed best to us to present the subject in the following order: First we shall report our own case. Then we shall present a review of the history and literature of the disease, with special attention to a résumé of the opinions that have been entertained with respect to its true nature. We will then give the opinion that we have formed on this point as the result of our study. The various analyses of the collected data will then be considered in detail under the usual headings of frequency and geographical distribution, etiology, pathology, clinical course, symptoms, complications, diagnosis, prognosis and treatment. In each instance, the consideration of these subsidiary topics will be concluded by giving the interpretation of the findings that has led us to form our opinion on the nature of the disease. In conclusion, we shall present a brief summary of the whole subject.

REPORT OF CASE

On July 24, 1925, Mrs. L. M., aged 20, a primipara, who was four months pregnant, first came under observation. The family history was unimportant. The patient had had the usual diseases of childhood, with the exception of scarlet fever and diphtheria. The previous history was otherwise irrelevant, except for the statement that she had been "nervous." The menstrual history was normal. The pregnancy was normal, with no nausea or vomiting. Physical examination disclosed a tall, very well nourished and developed girl of good color; her usual weight was 130 pounds (59 Kg.). There were no devitalized teeth, but a few with cavities. The tonsils were not diseased. There was a slight systolic blow at the apex, but no evidence of cardiac disease; the blood pressure was 110 systolic and 56 diastolic.

The patient was next seen on August 14, when the blood pressure and urine were again normal. She complained of being "nervous," but appeared to be in perfect health. On August 25, the patient was again seen, and a diagnosis of chorea could be made when she entered the room. She was constantly twitching, jumping and grimacing, and the picture was altogether typical. At this time it first developed that the "nervousness" mentioned in her history had been a definite attack of chorea for which she had been treated by Dr. Noble P. Barnes two years previously, when she was 18 years of age. The patient was put to bed at home for a week, but, as there was no improvement, she was admitted to Columbia Hospital for Women on September 2 for observation and treatment.

At this time the condition was not alarming, except for the gloomy prognosis given in every textbook consulted. While the patient was awake, the movement was constant and general, but ceased during sleep. The patient was cheerful and not greatly alarmed. Dr. Barnes saw her with us and directed the medical treatment, which consisted of rest, a light diet, regulation of bowel function, triple bromides by mouth and large doses of salicylates by rectum. On September 9, sodium cacodylate was given intramuscularly, and on the eleventh, 0.9 Gm. of neoarsphenamine intravenously; morphine was given as needed. The condition, however, became slowly but progressively worse. The movements were more violent, and incoordination was so extreme that the patient could not feed herself; after attempting to do so, her bed would be surrounded by portions of food that had been thrown on the floor. Insomnia was troublesome; her morale became very low, and her body from head to foot was covered with bruises where she had struck herself on the bed. The movements were so violent that one of the attending physicians, seeing her for the first time, mistook the condition for an eclamptic convulsion. On September 14, we asked Dr. D. V. D. Stuart to see her with us, and he made the following notations on the chart:

"This patient presents:

"(1) Violent choreiform movements involving apparently all the voluntary musculature of the body excepting the external ocular muscles.

"(2) Pressure points of tenderness along course of left radial, circumflex, great sciatic and posterior tibial nerves. There is no demonstrable weakness of any of the muscle groups innervated by the above nerves.

"Impression—choreiform condition, not hysterical, due to the patient's pregnancy.

"Suggest termination of pregnancy."

Acting on this advice, a Wales bougie was introduced at noon on September 14, the pregnancy being then advanced to 5½ months. Labor was slow in starting, and delivery of a stillborn fetus did not occur until 3:30 p. m. on the sixteenth. It would be impossible to exaggerate the pitiable and terrible condition of this girl during the interval. She was placed in a padded bed from which she could not throw herself. No clothing could be kept on her, and most of the time she was stark naked. The movement was constant and violent to an unbelievable degree, at least a foot in the air at one moment, on her heels and occiput at the next, and at the next with her feet over her head banging against the head of the bed, inarticulate animal-like cries her only means of expression, deglutition almost impossible even for water, and yet quite conscious; she made an indelible impression on all who saw her.

The postpartum progress was shown by notations by Dr. Stuart as follows: September 19: "Patient's condition is not materially changed since induction of labor. There is less involvement of tongue and pharyngeal muscles than when first seen but choreiform movements are still general. Tenderness over nerve trunks, noted at first examination, is still present." September 24: "Choreiform movements much less marked. There is still some tenderness over course of left radial nerve and left posterior tibial; other nerve trunk tenderness has disappeared." From this time on improvement was steady and rapid, and the patient was discharged on the twenty-seventh. One month later, all movement had ceased, and one year later the patient presented the picture of health. We have just been informed, however, that the patient has recently had a mild recurrence of the chorea unassociated with pregnancy.

The whole course of the disease was afebrile with the exception of a transitory temperature of 102.4 F., three hours before delivery. The pulse range during hos-

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five-Hundred and Thirty American Obstetricians*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea¶	Fate of the Pregnancy	Result for Mother**	Result for Child††	Comment
1	1	Reidlin, 1696	..	..	..	Yes	....	....	.	.....	Spontaneous abortion	L	D	
2	2	Ungen, 1764	18	..	I	....	....	....	5	A.p. in ninth month	Spontaneous labor at term	L	..	
3	3	Hand, 1807	23	S	I	....	....	....	6	A.p.	Spontaneous labor at term	L	..	
4	4	Capuron, 1817	24	M	I	....	....	....	.	P.p.	Spontaneous labor at term	L	L	
5	5	Vogel, 1820	22	M	I	....	....	....	3	3 years p.p.	.....	L	D	
6	6	Frank, 1821	..	..	I	Yes	....	....	*	.....	Spontaneous abortion in fifth month	L	D	*Early in pregnancy
7	7	Prichard, 1824	..	..	..	....	....	....	.	.....	Spontaneous abortion	D	D	Autopsy: cerebral congestion
8	8	Jeffreys, 1825	17	M	I	....	....	....	2	A.p. in fourth month	.....	L	..	
9	9	Turner, 1828	23	M	I	....	....	....	2	A.p.	.....	L	..	
10	10	Bezold, 1839	19	M	I	....	....	....	*	.....	Spontaneous labor at term	L	..	*First half of pregnancy
11	11	Ingleby, 1840	..	..	I	Yes	..	....	6	A.p. in ninth month	.....	L	..	
12	12	Ingleby, 1840	..	..	..	....	....	....	4	P.p.	.....	L	..	
13	13	Ingleby, 1840	..	..	..	....	....	....	*	.....	.....	D	..	*Early in pregnancy
14	14	Ingleby, 1840	..	..	..	....	....	....	*	Until death	Died undelivered	D	D	*Early in pregnancy; ovum of third month found in uterus
15	15	Ingleby, 1840	..	..	..	....	....	....	.	.....	.....	D	..	
16	16	Ingleby, 1840	..	..	..	....	....	....	.	.....	.....	D	..	
17	17	Ingleby, 1840	..	..	..	....	....	....	9	.....	Spontaneous premature labor	D	..	Autopsy negative
18	18	Lee, 1842	23	..	II	....	....	Yes	.	Until death	Spontaneous abortion in sixth month	D	D	Fright; died 47 hours post partum; autopsy: vegetations on the heart valves
19	19	Trousseau, 1846	17	S	I	Yes	....	....	2	A.p. in fifth month	.....	L	..	
20	20	Lever, 1847	..	..	I	....	....	....	3	A.p. in fourth month	Spontaneous labor at term	L	L	

21	21	Lever, 1847	30	..	III	Yes	....	..	*	P.p.	Spontaneous labor at term	L	..	*Chorea developed after miscarriage in fifth month of second pregnancy and was present when third pregnancy began
22a	22	Lever, 1847	19	M	I	No	....	..	3	1 month p.p.	Spontaneous labor at term	L	L	Chorea improved immediately post partum
b	23	Lever, 1847	..	M	II	Yes	....	....	*	2 weeks p.p.	Spontaneous abortion in fourth month	L	D	*Before third month; fright supposed to have caused abortion
23	24	DuBois, 1848	19	..	I	No	....	....	2	A.p.	Spontaneous labor at term	L	..	
24	25	Helft, 1848	20	S	I	Yes	....	....	1	P.p.	Spontaneous abortion in fifth month	L	D	Fright preceded attack
25	26	Helft, 1848	23	M	II	....	....	....	3	P.p.	Spontaneous labor at term	L	..	
26a	27	Lever, 1848	24	M	II	....	....	....	5	Until labor	Spontaneous labor at term	L	..	Chorea ceased with first labor pains and did not recur
b	28	Lever, 1848	..	M	*	Yes	....	....	.	P.p.	Spontaneous labor at term	L	..	*Multipara; chorea less severe in this pregnancy
27	29	Sée, 1850	20	M	I	Yes	....	....	3	A.p. in sixth month	.....	L	..	No chorea in a subsequent pregnancy
28	30	Sée, 1850	20	M	I	Yes	?	....	9	A few days p.p.	Spontaneous labor at term	L	..	Pain in wrists during the attack of chorea
29	31	Sée, 1850	..	..	..	....	....	....	3	.....	.....	L	..	
30	32	Aran, 1851	20	M	II	No	....	....	5	Until death	Spontaneous abortion	D	D	Fright preceded attack; fever; autopsy negative
31	33	Romberg, 1851	20	S	I	Yes	....	....	1	6 weeks p.p.	Spontaneous abortion in sixth month	L	D	
32	34	Romberg, 1851	23	M	II	No	....	....	2	P.p.	Spontaneous labor at term	L	..	
33a	35	Romberg, 1851	18	M	I	Yes	....	....	*	A.p. in fifth month	Spontaneous labor at term	L	..	*Early in pregnancy
b	36	Romberg, 1851	19	M	II	Yes	....	....	*	.....	Spontaneous labor at term	L	..	*Second half of pregnancy; chorea did not recur in third pregnancy
34	37	Anderson, 1853	18	..	I	Yes	....	....	8	2 weeks p.p.	Spontaneous labor at term	L	D	Fetal death due to breech presentation
35	38	Duncan, 1854	33	M	I	Yes	....	....	4	A.p. in eighth month	Spontaneous labor at term	L	L	No albuminuria; chorea limited to lower extremities
36	39	Duncan, 1854	*	M	*	....	....	No	6	A.p.*	.....	L	..	*Middle aged woman; *multipara; *attack lasted twenty days; no albuminuria; choreiform movements limited to lower limbs and at night only
37	40	Austin, 1855	..	..	I	Yes	....	....	7	Until death	Spontaneous premature labor in seventh month	D	D	Death three days after onset of chorea and twenty-four hours post partum; eclampsia ?
38	41	Austin, 1855	..	..	..	Yes	....	....	.	.....	Spontaneous abortion in fifth month	D	D	
39	42	Scanzoni, 1855	24	M	I	....	....	....	4	P.p.	Spontaneous premature labor in ninth month	L	..	Chorea ceased after removal of pieces of placenta
40	43	Spiegelberg, 1858	28	M	II	No	No	....	*	P.p.	Spontaneous labor at term	L	L	*Middle third of pregnancy; chorea ceased immediately post partum, but recurred six weeks later

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea‡	Time of Recovery from Chorea‡	Fate of the Pregnancy	Result for Mother†	Result for Child†	Comment
41	44	Brannock, 1859	20	..	I	No	....	....	5	P.p.	Spontaneous labor at term	L	..	
42	45	Marcé, 1860	22	..	I	....	....	....	*	*	Spontaneous labor at term	L	L	*Chorea present before pregnancy began and continued post partum
43	46	Levick, 1862	35	..	V	No	....	....	4	.....	Spontaneous labor at term	L	L	
44	47	Levick, 1862	17	M	I	Yes	....	....	3	.....	Spontaneous abortion	L	D	Fright preceded attack
45	48	Levick, 1862	17	S	I	No	....	Yes	5	Until death	Died undelivered in sixth month	D	D	Autopsy: cerebral congestion and diseased heart valves
46	49	Mosler, 1862	24	..	II	Yes	....	....	3	P.p.	Spontaneous labor at term	L	..	
47	50	No name, 1862	26	M	III	....	....	Yes	2	Until death	Died undelivered in fourth month	D	D	Autopsy: diseased mitral valve
48	51	Snyers, 1863	19	..	II	No	No	....	3	A.p. in fourth month	Spontaneous labor at term	L	..	
49	52	Kirkes, 1863	20	M	II	No	No	Yes	4	Until death	Spontaneous abortion in fifth month	D	D	Autopsy: diseased heart valve
50	53	Kirkes, 1863	25	..	II	Yes	Yes	Yes	9	Until death	Spontaneous labor at term	D	L	Chorea began four days ante partum; death five days post partum; autopsy: congestion of meninges, endocarditis; first pregnancy normal
51	54	Nagel, 1863	18	..	..	....	....	....	8	Until death	Spontaneous labor at term	D	..	Death due to postpartum eclampsia
52	55	Ladé, 1863	23	M	I	No	No	....	4	A.p. in sixth month	.....	L	..	No albuminuria
53	56	Chambers, 1864	23	M	I	....	Yes	Yes	6	P.p.	Spontaneous labor at term	L	..	Chorea complicated by acute rheumatism and acute endocarditis
54	57	Woodman, 1865	18	M	I	Yes	Yes	Yes	4	A.p. in fifth month	Spontaneous labor at term	L	L	Chorea recurred slightly post partum; no albuminuria
55	58	Woodman, 1865	..	..	I	....	....	....	2	A.p.	Spontaneous premature labor in eighth month	L	..	Fright preceded attack
56	59	Hine, 1865	21	..	II	Yes	....	No	8	Until death	Spontaneous premature labor in eighth month	D	L	Emotional disturbance preceded onset of chorea; autopsy negative

56	59	Hine, 1865	21	..	II	Yes	....	No	8	Until death	Spontaneous premature labor in eighth month	D	L	Emotional disturbance preceded onset of chorea; autopsy negative
57	60	Kunschert, 1865	21	M	II	Yes	....	No	3	A.p. in fourth month	Spontaneous labor at term	L	L	
58	61	Kunschert, 1865	26	M	IV	....	*	Yes	9	Until death	Died undelivered in ninth month	D	D	*Chorea occurred during course of acute rheumatic attack complicating pregnancy; death evidently due to acute nephritis after repeated and prolonged chloroform narcosis
59	62	Fischl, 1865	25	M	III	No	No	No	3	3 days p.p.	Induced abortion in fourth month	L	D	Urine normal
60a	63	Dumont, 1865	..	M	I	Yes	No	....	.	.....	.....	L	..	Mild attack
b	64	Dumont, 1865	22	M	II	Yes	No	....	5	A.p. in sixth month	.....	L	..	Attack cleared up after three weeks of treatment
61a	65	Gubler and Dumont, 1865	..	M	I	Yes	Yes	....	.	.....	.....	L	..	
b	66	Gubler and Dumont, 1865	22	M	II	Yes	Yes	....	5	A.p. in sixth month	Spontaneous labor at term	L	..	
62	67	Jaccoud, 1867	23	M	..	....	....	....	3	A.p. in fifth month	.....	L	..	
63	68	Tuckwell, 1867	24	..	..	....	....	Yes	1	Until death	Died undelivered in fourth month	D	D	Autopsy negative except for diseased heart valves
64	69	Ogle, 1868	17	S	I	....	No	Yes	1	Until death	Died undelivered in fourth month	D	D	Autopsy: diseased heart valves
65	70	Ogle, 1868	..	..	..	....	....	....	3	.....	Died undelivered	D	D	Autopsy: congestion of meninges of spinal cord
66	71	Ogle, 1868	23	M	II	....	....	....	6	.....	Spontaneous abortion in sixth month	D	D	Death one day post partum; autopsy negative
67	72	Trousseau, 1868	20	..	..	No	....	....	.	A.p.	.....	L	..	Attack lasted twenty-seven days and was complicated by mental disturbance
68	73	Bedford, 1868	19	M	I	No	....	....	4	P.p.	Spontaneous labor at term	L	L	
69a	74	Thompson and Davis, 1868	18	M	I	Yes	No	....	.	.....	.....	L	..	
b	75	Thompson and Davis, 1868	20	M	II	Yes	No	Yes	6	3 weeks p.p.	Spontaneous premature labor in seventh month	L	..	
70a	76	Tait, 1868	24	..	I	Yes	Yes	....	4	P.p.	Spontaneous labor at term	L	L	Chorea ceased immediately post partum
b	77	Tait, 1868	..	..	II	Yes	Yes	....	*	P.p.*	Spontaneous labor at term	L	L	*Chorea began before fourth month and ceased immediately post partum
c	78	Tait, 1868	..	..	III	Yes	Yes	....	*	P.p.*	Spontaneous abortion in third month	L	D	*Chorea began before third month and ceased immediately post partum
d	79	Tait, 1868	27	..	IV	Yes	Yes	No	1	Until death	Induced abortion in fourth month	D	D	No albuminuria; autopsy: negative except for congestion of brain
71a	80	Barnes, 1869	..	M	II	Yes	....	....	.	.....	.....	L	D	No chorea in first pregnancy
b	81	Barnes, 1869	20	M	III	Yes	....	No	5	P.p.	Induced premature labor in seventh month	L	L	Puerperal mania developed, which persisted
72	82	Barnes, 1869 (Hufeland)	19	..	..	....	*	....	7	.....	.....	L	..	*Chorea followed by acute rheumatism
73	83	Barnes, 1869 (Hufeland)	..	..	..	....	*	....	.	.....	.....	L	..	*Chorea complicated by acute rheumatism
74	84	Barnes, 1869 (Furnes)	..	..	..	....	....	....	3	A.p.*	.....	L	..	*Chorea lasted twenty-seven days
75	85	Barnes, 1869 (Mayo)	..	..	..	....	....	....	4	A.p. in sixth month	Spontaneous labor at term	L	L	Fright preceded attack; baby had chorea at birth

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
76	86	Barnes, 1869 (Pye-Smith)	23	M	II	....	....	....	*	.....	Spontaneous labor at term	L	..	*Late in pregnancy; fright preceded attack
77	87	Barnes, 1869 (Woodman)	20	M	I	Yes	No	Yes	7	2 months p.p.	Spontaneous labor at term	L	L	
78	88	Barnes, 1869 (Woodman)	18	..	I	....	....	Yes	8	Until death	Spontaneous labor at term	D	D	Albuminuria throughout pregnancy; eclampsia
79	89	Davis, 1869	20	M	I	No	No	?	2	P.p.	Spontaneous abortion in fifth month	L	D	
80	90	Goodell, 1870	19	M	I	Yes	Yes	No	5	Until death	Accouchement forcé in eighth month	D	D	No albuminuria
81	91	Russell, 1870	21	M	I	No	....	....	1	.....	.....	..	..	
82	92	Weber, 1870	33	M	V	No	No	....	9	9 days p.p.	Spontaneous premature labor in ninth month	L	L	
83	93	Sieckel, 1870	23	M	III	Yes	....	....	*	A.p.	.....	L	..	*Middle of pregnancy; first and second pregnancies were normal
84	94	Sieckel, 1870	26	M	I	No	No	....	7	P.p.	Spontaneous labor at term	L	L	Second pregnancy was normal
85a	95	Sieckel, 1870	27	..	I	....	....	....	6	A.p. in ninth month	Spontaneous labor at term	L	L	
b	96	Sieckel, 1870	30	..	II	Yes	....	....	6	P.p.	Spontaneous labor at term	L	..	
86	97	Barnes, 1873	18	..	I	Yes	....	....	3	.....	.....	..	..	Fright preceded the attack
87a	98	Barnes, 1873	*	..	I	Yes	Yes	....	*	.....	Spontaneous labor at term	L	L	*Patient under 20 years of age; chorea developed early in pregnancy
b	99	Barnes, 1873	*	..	II	Yes	Yes	....	*	.....	.....	L	L	*Patient under 22 years of age; chorea developed early in pregnancy
c	100	Barnes, 1873	22	..	III	Yes	Yes	?	2	.....	.....	..	..	
88	101	Arnoldi, 1873	19	..	II	Yes	....	....	8	Until death	Spontaneous premature labor in ninth month	D	D	First pregnancy normal
89	102	Bamberg, 1873	36	M	IV	....	....	Yes	3	Until death	Died undelivered	D	D	First, second and third pregnancies normal; death sixteen days after onset of chorea; autopsy: diseased heart valves

90	103	Prentiss, 1874	25	M	II	No	No	....	5	A.p. in eighth month	Spontaneous labor at term	L	L	
91	104	Prentiss, 1874	25	M	..	No	No	....	4	A.p. in eighth month	Spontaneous labor at term	L	L	
92	105	Mackall, 1874	18	S	I	No	....	....	*	Until death	Died undelivered	D	D	*Onset of chorea when several months advanced in pregnancy
93	106	Fehling, 1874	23	..	I	No	....	....	7	3 weeks p.p.	Spontaneous premature labor in eighth month	L	D	
94a	107	Elischer, 1874	20	..	I	Yes	....	....	6	.....	Spontaneous labor at term	L	..	
b	108	Elischer, 1874	22	..	II	Yes	....	....	5	Until death	.....	D	..	For report of autopsy see text
95	109	Oulmont, 1875	28	M	I	No	Yes	?	2	A.p. in fourth month	.....	L	..	Slight albuminuria
96	110	Oulmont, 1875	25	..	..	....	....	....	1	A.p.	.....	L	..	
97	111	Fasbender, 1875	23	..	I	No	Yes	Yes	9	P.p.	Spontaneous labor at term	L	L	
98	112	Prince, 1875	20	M	I	....	....	....	4	Until death	Died undelivered	D	D	Death three days after onset of chorea; morphine, 1 grain, given; death due to morphine ?
99	113	Simpson, 1875	20	S	..	....	Yes	No	3	Until death	Died undelivered	D	D	Death in fifth month of pregnancy; autopsy negative
100	114	Schwechten, 1876	24	..	I	Yes	....	....	*	P.p.	.....	L	..	*Chorea since 7 years of age; present when pregnancy occurred
101	115	Schwechten, 1876	22	M	I	Yes	....	....	*	A.p.	Spontaneous labor at term	L	L	*Onset of chorea in first half of pregnancy
102	116	Schwechten, 1876	19	..	..	Yes	....	....	6	A.p.	.....	L	L	
103a	117	Schwechten, 1876 (Fieber)	..	..	I	....	....	....	*	A.p.	.....	L	..	*Early in pregnancy
b	118	Schwechten, 1876 (Fieber)	23	..	II	Yes	....	....	2	A.p. in third month	.....	L	..	
104	119	Dickinson, 1876	17	S	..	No	No	Yes	1	Until death	Died undelivered in fourth month	D	D	Autopsy; cerebral congestion and mitral disease
105	120	Lyman, 1877	30	S	..	....	....	....	2	.....	.....	..	..	
106	121	Lyman, 1877	18	S	..	Yes	....	....	*	.....	.....	..	..	
107	122	Richardson, 1877	17	..	I	Yes	....	....	*	P.p.*	Spontaneous labor at term	L	..	*Chorea was present when pregnancy occurred, but ceased immediately post partum
108	123	Richardson, 1877	22	..	II	Yes	....	....	6	5 days p.p.	Spontaneous labor at term	L	..	No chorea in first pregnancy
109	124	Hazard, 1877	22	..	..	....	....	....	*	P.p.*	Spontaneous labor at term	L	L	*Chorea developed late in pregnancy and persisted for months post partum
110	125	Hazard, 1877	..	S	..	No	....	....	9	3 weeks p.p.	Spontaneous labor at term	L	L	
111	126	Swift, 1878	23	S	I	Yes	....	....	2	Few days p.p.	Spontaneous labor at term	L	L	
112	127	Edgerly, 1878	24	*	II	No	Yes	....	3	A.p. in fifth month	Spontaneous labor at term	L	L	*Patient was married; pregnancy was illegitimate, however
113	128	Edgerly, 1878	19	S	I	Yes	Yes	....	1	P.p.	Spontaneous labor at term	L	..	
114	129	Hamilton, 1878	24	..	..	....	....	....	6	3 weeks p.p.	Spontaneous labor at term	L	L	Fright
115	130	Wade, 1880	19	S	I	....	Yes	?	6	P.p.	Spontaneous labor at term	L	L	Cervix dilated twice, under chloroform, in the seventh month, to cure the chorea, which was better but persisted until post partum

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
116	131	Sawyer, 1880	25	..	II	....	....	....	.	Until death	Spontaneous abortion in sixth month	D	D	Fright; died two days post partum
117a	132	Edge, 1880	..	M	I	....	....	....	.	.....	.....	L	..	
b	133	Edge, 1880	..	M	II	Yes	....	....	.	.....	.....	L	..	
c	134	Edge, 1880	..	M	III	Yes	....	....	.	.....	.....	L	..	
d	135	Edge, 1880	27	M	IV	Yes	Yes	?	4	P.p.	Spontaneous abortion in fourth month	L	D	
118a	136	Edge, 1880	18	M	I	No	Yes	....	2	P.p.	Spontaneous labor at term	L	..	
b	137	Edge, 1880	..	M	II	Yes	Yes	....	.	P.p.	Spontaneous labor at term	L	..	
c	138	Edge, 1880	..	M	III	Yes	Yes	....	.	P.p.	Spontaneous labor at term	L	..	
119	139	Ahlfeld, 1881	23	..	I	No	Yes	No	5	2 weeks p.p.	Induced abortion in sixth month	L	D	
120	140	Mackenzie, 1881	27	..	..	Yes	No	Yes	.	.....	.....	D	..	Autopsy: diseased heart valves
121	141	Sturges, 1881	21	M	I	No	Yes	?	2	A.p. in ninth month	.....	L	..	
122	142	Groeschner, 1881	22	M	II	No	No	No	3	P.p.	Induced abortion in fourth month	L	D	First pregnancy normal
123	143	Bastian, 1881	24	M	I	Yes	....	....	5	A.p. in seventh month	Spontaneous labor at term	L	L	
124	144	Mundé, 1882	23	M	III	....	....	....	7	P.p.	Spontaneous labor at term	L	L	Puerperal mania
125	145	Shtshetkin, 1882	26	M	VI	No	....	....	5	A.p.*	Spontaneous labor at term	L	L	*First attack lasted two days; slight return in ninth month; probably hysteria
126	146	Sommerbrodt, 1882	25	..	I	....	....	Yes	.	.....	.....	D	..	Placenta previa; death one day post partum; autopsy: endometritis and myocarditis
127	147	Vassitch, 1883	20	M	I	Yes	....	....	3	1 day p.p.	Spontaneous labor at term	L	L	
128	148	Vassitch, 1883	22	S	I	....	....	....	1	.....	.....	..	..	Mental disturbance
129	149	Behnicke, 1883	..	..	II							L	..	

130a	150	Beinicke, 1883			*	....				P.p.		L		
b	151	Beinicke, 1883			*	Yes				P.p.		L		*Multipara
c	152	Beinicke, 1883			*	Yes				P.p.		L		*Multipara
d	153	Beinicke, 1883			*	Yes				P.p.		L		*Multipara
131	154	Perego, 1885	25	M	IV	....	*	?	2	A.p. in seventh month	Spontaneous labor at term	L	L	*Rheumatism complicating the chorea
132	155	Muleur, 1884	*	..	I	Yes	....	No	*	Until death	Died undelivered in fourth month	D	D	*Patient between 18 and 20 years of age; *onset of chorea early in pregnancy; autopsy negative
133	156	Brouardel, 1884	18	..	I	Yes	No	....	1	A.p. in seventh month	.....	L	..	
134a	157	Olshausen, 1884	21	M	I	Yes	....	....	.	A.p.	Spontaneous labor at term	L	..	
b	158	Olshausen, 1884	23	M	II	Yes	....	Yes	*	Until death	Induced labor in ninth month	D	D	*Onset of chorea early in pregnancy; continuous chloroform narcosis for twenty-four hours; autopsy: effusion under arachnoid, pneumonia
135	159	Stephann, 1885	21	..	I	....	....	....	9	.....	.....	..	..	
136	160	Miles, 1885	23	M	*	....	....	....	5	Until death	Died undelivered	D	D	*Multipara; death about one week after onset of chorea; mania; high fever
137a	161	Young, 1885	..	M	I	Yes	....	....	.	P.p.	Spontaneous abortion in sixth month	L	D	
b	162	Young, 1885	23	M	II	Yes	....	....	1	A.p. in ninth	Spontaneous labor at term	L	..	
138	163	Churton, 1886	24	S	..	..	....	....	3	A.p.	.....	L	..	Emotional disturbance preceded attack
139	164	Churton, 1886	20	M	..	Yes	....	....	2	P.p.	.....	L	L	
140	165	Churton, 1886	22	..	..	Yes	....	..	3	Few days p.p.	Induced abortion in fifth month	L	D	
141	166	Churton, 1886	..	..	..	....	....	....	.	.....	.....	D	..	
142	167	Charles, 1886	23	S	I	....	....	....	.	Until death	Accouchement forcé in seventh month	D	D	Patient moribund at time of operation; died at once; no albuminuria
143	168	Pollock, 1886	20	S	..	No	No	....	4	5 weeks p.p.	Induced abortion in fifth month	L	D	
144	169	Litten, 1886	..	..	I	....	Yes	....	3	.....	.....	..	..	Acute rheumatism immediately before onset of chorea
145	170	Litten, 1886	23	M	II	Yes	Yes	Yes	4	.....	.....	..	L	Rheumatism and acute endocarditis just before onset of chorea
146	171	Litten, 1886	22	M	I	Yes	*	*	4	.....	Spontaneous labor at term	..	L	*Chorea, acute rheumatism and endocarditis at the same time
147	172	Litten, 1886	24	S	II	....	*	*	3	.....	Spontaneous labor at term	..	L	*Chorea, acute rheumatism and endocarditis at the same time
148	173	Litten, 1886	20	M	I	Yes	....	....	1	A.p. in third month	Spontaneous labor at term	L	..	
149	174	Litten, 1886	..	..	I	....	Yes	Yes	4	P.p.	Spontaneous labor at term	L	L	Rheumatism just before onset of chorea, which was complicated by acute endocarditis
150	175	Litten, 1886	20	..	I	....	....	....	3	P.p.	Spontaneous abortion	L	D	
151	176	Litten, 1886	23	M	III	....	....	....	3	P.p.	Induced abortion in fourth month	L	D	
152	177	Litten, 1886	..	.	I	....	....	....	9	Until death	Induced labor in ninth month	D	..	Death one day post partum; autopsy: serous effusion over the brain
153	178	Litten, 1886	23	S	I	....	*	Yes	*	Until death	Spontaneous abortion in third month	D	D	*Onset of chorea prior to third month; autopsy: acute endocarditis, general septicemia and purulent effusion in the joints

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea¶	Fate of the Pregnancy	Result for Mother#	Result for Child#	Comment
154	179	Litten, 1886	17	S	..	....	....	Yes	.	.....	Died undelivered	D	D	Autopsy: recent endocarditis
155	180	Guinon, 1886	19	S	..	Yes	Yes	Yes	2	Until death	Died undelivered in fourth month	D	D	Autopsy: recent endocarditis, bronchial pneumonia, "absolute integrity of the central nervous system"
156a	181	Schuhl, 1886	..	M	I	Yes	No	....	3	A.p. in fifth month	Spontaneous premature labor	L	L	
b	182	Schuhl, 1886	20	M	II	Yes	No	....	4	A.p. in seventh month	Spontaneous labor at term	L	L	Onset of chorea after violent emotion; albuminuria
157a	183	Schweiger, 1886	..	M	I	Yes	....	....	.	P.p.	.....	L	..	
b	184	Schweiger, 1886	25	M	II	Yes	....	....	2	P.p.	.....	L	..	
158	185	Koch, 1887	27	M	I	Yes	....	....	2	P.p.	Spontaneous abortion in fourth month	L	D	
159	186	Koch, 1887	19	..	..	Yes	Yes	Yes	6	P.p.*	Spontaneous premature labor	L	D	*Chorea ceased immediately post partum
160	187	Talent, 1887	17	S	I	Yes	Yes	No	6	P.p.	Induced premature labor in seventh month	L	L	
161	188	Kemper, 1887	23	M	II	....	Yes	....	4	Until death	Died undelivered	D	D	Fright preceded attack; fever
162	189	Volquardsen, 1887	21	M	I	....	....	....	5	A.p.	Spontaneous labor at term	L	..	
163	190	Wasseige, 1887	23	M	I	....	....	....	7	Until death	Accouchement forcé	D	D	Fright preceded attack; death a few hours post partum
164	191	Mackenzie, 1887 (Treharne)	19	S	I	No	Yes	....	5	1 month p.p.	Spontaneous abortion in sixth month	L	D	Fright preceded attack; abortion two weeks after onset of chorea
165	192	Mackenzie, 1887 (Dobie)	20	M	I	Yes	Yes	No	4	1 month p.p.	Spontaneous abortion in sixth month	L	D	Puerperal mania in puerperium with recovery
166	193	Mackenzie, 1887 (Pearce)	26	M	II	Yes	....	....	.	.....	.....	L	..	
167	194	Mackenzie, 1887 (Thursfield)	24	M	I	Yes	Yes	No	2	Until death	Induced premature labor in eighth month	D	D	
168	195	Mackenzie, 1887 (Benthall)	23	..	II	No	Yes	No	.	A.p.*	Spontaneous labor at term	L	..	*Chorea lasted eight weeks
169	196	Mackenzie, 1887 (Handford)	19	..	..	Yes	Yes	Yes	.	.....	.....	L	..	

169	196	Mackenzie, 1887 (Handford)	19	..	..	Yes	Yes	Yes	.		at term	L		
170a	197	Mackenzie, 1887 (Davis)	23	M	I	Yes	No	No	1	A.p. in seventh month	Spontaneous labor at term	L	L	Worry before onset of chorea
b	198	Mackenzie, 1887 (Davis)	..	M	II	Yes	No	....	.	.....	Spontaneous labor at term	L	..	
171	199	Lehmann, 1887	23	S	I	No	No	....	7	A.p.*	Spontaneous labor at term	L	L	*Chorea lasted two weeks during pregnancy, but relapsed in the second month post partum and lasted four months
172	200	Lehmann, 1887	30	M	VI	No	....	....	5	Until death	Died undelivered in seventh month	D	D	Autopsy negative
173	201	Lehmann, 1887	21	M	I	....	....	Yes	5	Until death	Spontaneous abortion	D	D	Autopsy: bronchial pneumonia and myocarditis
174	202	Thursfield, 1887	20	M	III	Yes	No	?	5	Until death	Induced abortion in fifth month	D	D	Death on eleventh day post partum; marked albuminuria
175	203	Dodge, 1888	23	M	III	No	No	....	6	In second month p.p.	Spontaneous labor at term	L	..	Chorea complicated by epilepsy
176	204	Hirst, 1888	18	M	I	....	....	....	3	A.p. in ninth month	Induced premature labor*	L	L	*Labor induced for puerperal mania
177	205	Hirst, 1865	19	..	I	Yes	No	No	1	15 days p.p.	Spontaneous labor at term	L	L	
178	206	Tait, 1888	21	S	..	Yes	Yes	No	2	P.p.	Induced premature labor in eighth month	L	D	
179	207	Goodell, 1888	..	..	..	....	....	....	.	.....	.....	L	..	
180	208	Hocquet, 1888	25	..	..	Yes	....	....	3	A.p. in eighth month	.....	L	..	Chorea complicated by hysteria
181	209	Hocquet, 1888	18	..	I	Yes	....	No	3	P.p.	Spontaneous labor at term	L	L	
182	210	Walker, 1888	20	..	..	....	....	....	*	.....	.....	..	..	*Onset of chorea before fourth month
183	211	No name, 1888	..	..	..	....	....	....	.	A.p.	.....	L	..	Recovery followed application of iodine to cervix
184	212	Benedict, 1888	20	M	I	Yes	....	....	3	A.p. in fifth month	.....	L	..	
185	213	Marshall, 1888	18	S	I	Yes	....	....	*	P.p.	Spontaneous labor at term	L	L	*Patient had chorea before pregnancy occurred
186a	214	Marshall, 1888	20	M	I	No	....	....	.	*	Spontaneous labor at term	L	L	*Chorea continued post partum
b	215	Marshall, 1888	22	M	II	Yes	....	....	*	*	Spontaneous labor at term	L	D	*Chorea had persisted since first pregnancy; fetal death due to breech presentation
c	216	Marshall, 1888	23	M	III	Yes	....	....	*	*	Spontaneous labor at term	L	L	*Chorea continuously since first pregnancy; and persisted post partum
187a	217	Sherman, 1888	..	M	I	....	....	....	.	P.p.	Spontaneous labor at term	L	L	
b	218	Sherman, 1888	..	M	II	Yes	....	....	.	P.p.	Spontaneous labor at term	L	L	
188	219	Handfield-Jones, 1889	25	M	I	No	No	No	4	3 weeks p.p.	Induced abortion in sixth month	L	D	Fright preceded attack; acute mania
189	220	Handfield-Jones, 1889	19	M	I	....	No	No	1	A.p. in fourth month	Spontaneous labor at term	L	L	
190	221	Charpentier, 1889	19	..	I	....	....	....	3	A.p. in eighth month	Spontaneous labor at term	L	L	
191	222	Charpentier, 1889	20	..	I	Yes	....	....	5	A.p. in seventh month	Spontaneous labor at term	L	L	

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
192	223	Charpentier, 1889 (Hallopeau)	18	..	I	....	....	....	.	.....	.....	..	..	
193	224	Ruhemann, 1889	20	..	..	Yes	Yes	No	2	A.p.	Spontaneous labor at term	L	..	
194	225	Ruhemann, 1889	20	M	II	Yes	No	....	2	A.p. in fourth month	Spontaneous labor at term	L	L	First pregnancy ended in abortion in second month; no chorea in this pregnancy
195 *	226	Ruhemann, 1889	20	M	..	....	....	....	1	2 weeks p.p.	Induced premature labor in seventh month	L	D	Mental disturbance
196a	227	Ruhemann, 1889	21	..	I	Yes	....	....	1	A.p. in fourth month	Spontaneous labor at term	L	L	
b	228	Ruhemann, 1889	23	..	II	Yes	....	....	1	.....	Spontaneous labor at term	L	..	
197a	229	Ruhemann, 1889	..	M	I	....	....	....	7	.....	.....	L	..	Second pregnancy was free from chorea
b	230	Ruhemann, 1889	25	M	III	Yes	....	....	5	Until death	Induced premature labor in seventh month	D	D	Autopsy: endometritis, colpitis, nephritis and hepatitis
198	231	Lloyd, 1889	*	M	I	....	....	....	3	.....	.....	..	..	*Young woman
199a	232	Huet, 1889	21	M	I	No	No	....	*	15 to 20 days p.p.	Spontaneous labor at term	L	..	*Early in pregnancy
b	233	Huet, 1889	23	M	II	Yes	No	....	3	1 month p.p.	Spontaneous labor at term	L	..	
c	234	Huet, 1889	24	M	III	Yes	No	....	2	*	Spontaneous labor at term	L	..	*Chorea persisted post partum
d	235	Huet, 1889	30	M	IV	Yes	No	....	*	*	Spontaneous premature labor in seventh month	L	..	*Chorea present when this pregnancy began and continued with slight intermission until patient's death in her sixty-eighth year; autopsy: no evidence of abnormality of the central nervous system
200	236	Steinkopff, 1890	24	M	IV	....	....	Yes	3	Until death	Died undelivered in fourth month	D	D	Autopsy: endocarditis
201	237	Hensoldt, 1890	25	..	II	....	*	Yes	.	P.p.	Spontaneous labor at term	L	L	*Acute articular rheumatism complicating the chorea
202	238	Hensoldt, 1890	28	..	IV	....	....	....	2	P.p.	Spontaneous labor at term	L	L	

203a	239	Pantzer, 1890	..	M	III	No	Yes	....	7	2 months p.p.	Induced premature labor in eighth month	L	..	First two pregnancies free from chorea
b	240	Pantzer, 1890	..	M	IV	Yes	Yes	....	9	.....	.....	L	..	
c	241	Pantzer, 1890	26	M	V	Yes	Yes	?	6	9 days p.p.	Spontaneous labor at term	L	L	
204a	242	Bonnaud, 1890	..	..	..	....	....	No	3	1 or 2 months p.p.	Spontaneous labor at term	L	..	
b	243	Bonnaud, 1890	..	..	*	Yes	....	No	3	1 or 2 months p.p.	Spontaneous labor at term	L	..	*Multipara
c	244	Bonnaud, 1890	..	..	*	Yes	....	No	3	1 or 2 months p.p.	Spontaneous labor at term	L	..	*Multipara
205a	245	Hubert, 1890	..	..	I	....	....	....	.	.....	.....	L	..	
b	246	Hubert, 1890	..	..	II	Yes	....	....	7	A.p.	Spontaneous labor at term	L	L	Chorea ceased following dilatation of the cervix
206	247	Hicks, 1891	..	S	I	Yes	....	?	*	P.p.	Spontaneous labor at term	L	..	*Chorea present when pregnancy began; albuminuria
207	248	McCann, 1891	23	M	I	Yes	Yes	?	*	3 days p.p.	Spontaneous labor at term	L	L	*Chorea present when pregnancy began; patient was epileptic
208	249	McCann, 1891	26	M	II	No	No	....	2	6 days p.p.	Induced premature labor in eighth month	L	L	First pregnancy normal
209a	250	McCann, 1891	20	M	I	Yes	No	....	5	P.p.	Spontaneous labor at term	L	L	
b	251	McCann, 1891	21	M	II	Yes	No	?	3	5 months p.p.	Spontaneous labor at term	L	L	
210	252	McCann, 1891 (Grigg)	17	M	I	Yes	Yes	....	4	P.p.	Spontaneous labor at term	L	L	No albuminuria
211	253	McCann, 1891 (Hope)	26	S	I	No	?	?	5	P.p.	Spontaneous labor at term	L	L	No remarks
212	254	Cameron, 1891	31	M	III	....	....	?	3	.....	Spontaneous labor at term	L	L	No albuminuria
213	255	Hensoldt, 1891	15	..	I	Yes	Yes	....	2	P.p.	Spontaneous labor at term	L	L	
214	256	Hensoldt, 1891	26	..	I	....	....	Yes	2	*	Spontaneous labor at term	L	..	*Chorea persisted post partum
215	257	Riche, 1891	26	M	VI	No	No	No	2	4 days p.p.	Spontaneous premature labor in seventh month	L	D	Fright preceded attack; baby lived only fifteen days
216	258	Riche, 1891	23	..	I	Yes	Yes	?	.	.....	Spontaneous labor at term	L	L	
217	259	Riche, 1891	22	..	I	No	No	?	5	P.p.	Spontaneous labor at term	L	D	
218a	260	Riche, 1891	21	..	I	Yes	Yes	....	1	A.p. in fifth month	.....	L	..	
b	261	Riche, 1891	24	..	II	Yes	Yes	....	1	A.p. in fifth month	.....	L	L	
219a	262	Riche, 1891	..	M	I	No	No	....	2	8 days p.p.	Spontaneous labor at term	L	..	
b	263	Riche, 1891	..	M	II	Yes	No	....	2	P.p.*	Spontaneous labor at term	L	L	*Chorea ceased immediately after an attack of post partum eclampsia
c	264	Riche, 1891	..	M	III	Yes	No	....	2	8 days p.p.	Spontaneous abortion in fourth month	L	D	
d	265	Riche, 1891	..	M	IV	Yes	No	...	2	8 days p.p.	Spontaneous abortion in fourth month	L	D	

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
e	266	Riche, 1891	27	M	V	Yes	No	No	5	3 days	Spontaneous premature labor in eighth month	L	L	
220	267	Didier, 1892	26	S	I	No	No	?	9	Few days p.p.	Spontaneous labor at term	L	L	No albuminuria
221	268	Turner, 1892	19	M	..	....	No	?	2	Until death	Induced abortion in fourth month	D	D	Autopsy negative, but patient evidently died of puerperal infection
222	269	Marx, 1892	23	*	I	No	No	....	1	2 weeks p.p.	Spontaneous premature labor in seventh month	L	..	*Pregnancy antedated marriage; urine normal
223	270	Marx, 1892	20	..	I	Yes	Yes	....	3	10 days p.p.	Spontaneous labor at term*	L	D	*Craniotomy; urine normal
224	271	Friis, 1892	24	..	..	Yes	....	?	3	Until death	Died undelivered in fifth month	D	D	Autopsy negative; albuminuria
225	272	Friis, 1892	27	M	..	....	....	....	5	.....	.....	..	..	
226	273	Schwarze, 1892	20	..	I	....	....	....	8	*	Spontaneous labor at term	L	..	*Chorea persisted post partum, as long as patient was under observation
227	274	Schwarze, 1892	22	..	I	....	....	....	6	P.p.	Spontaneous premature labor	L	..	
228	275	Walls, 1892	19	M	I	No	No	Yes	6	Until death	Induced premature labor in seventh month	D	D	Autopsy negative except for acute endocarditis
229	276	Lloyd, 1893	22	S	I	Yes	....	....	*	P.p.	.....	L	..	*Chorea present when pregnancy began
230	277	Lloyd, 1893	39	M	V	No	....	....	*	*	.....	L	..	*Chorea present when pregnancy began and was still present five years post partum
231	278	Hünermann, 1893	18	..	I	....	Yes	No	1	.....	Spontaneous premature labor	L	L	
232	279	Fontenau, 1893	19	..	I	No	....	....	2	19 days p.p.	Spontaneous abortion in third month	L	D	
233	280	Fontenau, 1893	19	..	I	....	....	....	5	18 days p.p.	Spontaneous premature labor	L	D	Chorea complicated by hysteria
234	281	Fontenau, 1893	19	S	I	No	....	....	5	10 days p.p.	Spontaneous labor at term	L	L	Emotional disturbance preceded the onset of the chorea
235	282	Fontenau, 1893	20	S	I	No	....	....	7	.....	.....	..	..	
236a	283	Fontenau, 1893	18	..	I	No	....	....	2	A.p. in fourth month	Spontaneous premature labor in eighth month	L	D	

236a	283	Fontenau, 1893	18	..	I	No	....	....	2	A.p. in fourth month	Spontaneous premature labor in eighth month	L	L	
b	284	Fontenau, 1893	19	..	II	Yes	....	?	1	.....	.....	..	..	
237a	285	Fontenau, 1893	17	..	I	Yes	....	....	3	A.p. in sixth month	.....	L	..	
b	286	Fontenau, 1893	18	..	II	Yes	....	....	8	.....	Spontaneous premature labor in eighth month	L	..	
238a	287	Puech, 1893	23	..	I	No	....	....	.	1 month p.p.	Spontaneous labor at term	L	..	
b	288	Puech, 1893	24	..	II	Yes	....	....	1	1 month p.p.	Spontaneous labor at term	L	L	
239a	289	Brenton, 1893	19	..	I	Yes	Yes	....	.	A.p.	.....	L	D	
b	290	Brenton, 1893	20	..	II	Yes	Yes	....	1	.....	.....	..	..	
240	291	Eberson, 1894	23	M	I	....	....	....	7	P.p.	Spontaneous labor at term	L	L	
241	292	Davis, 1894	21	M	I	Yes	....	No	3	Until death	Induced abortion in third month	D	D	Fever; marked albuminuria; death twenty hours post partum
242	293	Beulque. 1894	24	M	II	....	....	....	6	P.p.	Spontaneous labor at term	L	L	Onset of chorea just after beating by husband; no albuminuria
243	294	Beulque, 1894	23	..	I	No	....	No	3	10 days p.p.	Spontaneous premature labor	L	D	Second pregnancy normal
244	295	Beulque, 1894	20	..	I	....	....	....	4	3 days p.p.	Spontaneous premature labor	L	L	Patient epileptic
245	296	Hochstetter, 1894	18	..	I	....	....	....	4	P.p.	Spontaneous labor at term	L	L	
246	297	Osler, 1894	20	M	I	Yes	....	....	.	.....	.....	..	..	
247	298	Osler, 1894	22	M	..	Yes	....	....	.	.....	.....	..	..	
248	299	Osler, 1894	21	M	..	Yes	....	....	*	.....	.....	..	..	*Early in pregnancy
249	300	Osler, 1894	30	..	..	Yes	....	....	4	.....	.....	D	..	
250	301	Buist, 1895	21	M	II	No	No	....	7	*	Spontaneous labor at term	L	L	*Chorea was still present two months post partum
251a	302	Buist, 1895 (Croom)	25	M	I	No	No	....	3	.....	Spontaneous abortion in fifth month	L	D	
b	303	Buist, 1895 (Croom)	26	M	II	Yes	No	....	3	.....	Spontaneous premature labor in seventh month	L	D	
c	304	Buist, 1895 (Croom)	27	M	III	Yes	No	....	1	P.p.	Spontaneous labor at term	L	L	
d	305	Buist, 1895 (Croom)	29	M	IV	Yes	No	Yes	1	P.p.	Spontaneous premature labor in seventh month	L	D	
e	306	Buist, 1895 (Croom)	..	M	V	Yes	No	....	.	P.p.	Spontaneous abortion in third month	L	D	
252a	307	Buist, 1895 (Affleck)	20	M	I	Yes	....	....	.	A.p.	.....	L	..	
b	308	Buist, 1895 (Affleck)	..	M	II	Yes	....	....	.	.....	.....	L	..	
c	309	Buist, 1895 (Affleck)	24	M	III	Yes	....	?	.	A.p.	.....	L	..	
253	310	Buist, 1895 (Felkin)	19	M	I	No	No	?	5	A.p.*	.....	L	..	*Chorea attributed to dyspareunia; ceased after hymen was incised
254	311	Buist, 1895 (Felkin)	..	..	III	No	....	....	.	A.p.*	.....	L	..	*Chorea ceased after removal of urethral caruncle
255	312	Buist, 1895 (Still)	26	M	II	No	No	?	6	3 months p.p.	Spontaneous labor at term	L	L	First pregnancy normal; no albuminuria
256	313	Arai, 1895	24	M	I	....	....	....	5	P.p.	Induced abortion in fifth month	L	D	

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child‖	Comment
257	314	Lantos, 1895	24	M	IV	Yes	....	....	2	P.p.	Induced abortion in third month	L	D	No chorea or hyperemesis in first three pregnancies
258a	315	Haultain, 1895	..	..	I	....	....	....	.	.....	.....	L	..	
b	316	Haultain, 1895	..	..	II	Yes	....	....	1	P.p.	Spontaneous labor at term	L	..	
259a	317	Crouch, 1895	..	M	I	No	....	....	8	Few days p.p.	Spontaneous labor at term	L	..	
b	318	Crouch, 1895	..	M	II	Yes	....	....	.	P.p.	Spontaneous labor at term	L	..	
c	319	Crouch, 1895	..	M	III	Yes	....	....	.	P.p.	Spontaneous labor at term	L	..	
d	320	Crouch, 1895	32	M	IV	Yes	....	....	.	P.p.	Spontaneous labor at term	L	L	
e	321	Crouch, 1895	35	M	V	Yes	....	....	.	15 days p.p.	Spontaneous labor at term	L	..	
260	322	von Bechterew, 1896	..	..	..	....	....	....	.	.....	.....	D	..	
261	323	Kroner, 1896	20	..	I	No	No	No	4	2 weeks p.p.	Induced abortion in fifth month	L	D	
262	324	Tinley, 1896	28	S	I	Yes	Yes	No	*	Until death	Induced abortion in fifth month	D	D	*Chorea began before third month; death on second day post partum
263	325	Catherson, 1896	20	M	II	Yes	....	....	*	Until death	Spontaneous labor at term	D	..	*Chorea began on second day post partum; high fever; death in forty-eight hours
264	326	Flynn, 1896	..	M	..	Yes	Yes	?	3	A.p. in eighth month	Spontaneous labor at term	L	L	No albuminuria
265	327	Flynn, 1896	21	M	I	No	Yes	?	2	A.p. in fifth month	Spontaneous premature labor in eighth month	L	D	Baby stillborn
266	328	Milligan, 1896	26	M	I	....	....	Yes	2	Until death	Spontaneous labor at term	D	..	Death on sixth day post partum; autopsy: endocarditis, embolism of the middle cerebral artery and rupture of small branch of same vessel
267a	329	Cameron, 1896	27	M	III	Yes	Yes	....	*	P.p.	Spontaneous labor at term	L	L	*Chorea began before sixth month
b	330	Cameron, 1896	30	M	IV	Yes	Yes	....	7	P.p.	Spontaneous labor at term	L	L	

267a	329	Cameron, 1896	27	M	III	Yes	Yes	....	....	P.p.	Spontaneous labor at term	L	L
b	330	Cameron, 1896	30	M	IV	Yes	Yes	....	7	P.p.	Spontaneous labor at term	L	L
268	331	Festenberg, 1897	26	M	III	No	....	No	2	4 days p.p.	Induced abortion in fifth month	L	D	First two pregnancies normal; no albuminuria; acute mania complicating the chorea
269	332	Collier, 1897	21	M	II	Yes	No	No	*	P.p.	Induced abortion in fifth month	L	D	*Chorea for two months before conception; fright preceded attack; improvement immediately after abortion
270	333	Dakin, 1897	22	M	II	No	No	Yes	.	Until death	Died undelivered in fifth month	D	D	First pregnancy normal; attempt to induce abortion failed; chloroform; autopsy: cloudy swelling of viscera
271	334	Dakin, 1897	23	M	I	Yes	....	Yes	4	Until death	Induced abortion in fifth month	D	D	Attack lasted four days; chloroform; autopsy; cloudy swelling of the vicera
272	335	Dakin, 1897	18	S	I	No	Yes	?	2	P.p.*	Induced abortion in sixth week	L	D	*Chorea still present slightly one month post partum; mania; no albuminuria
273	336	Dakin, 1897	23	M	I	....	....	?	6	2 months p.p.	Induced premature labor in seventh month	L	L	Chorea complicated by mania
274	337	Dakin, 1897	23	S	I	Yes	Yes	Yes	6	2 weeks p.p.	Induced abortion in sixth month	L	D	Chorea complicated by mania
275	338	Dakin, 1897	23	M	V	No	No	....	2	.....	.....	..	..	
276	339	Dakin, 1897	19	M	I	Yes	....	?	*	A.p.	.....	L	..	*Chorea began before third month and lasted one month
277	340	Velde and Volkmann, 1898	21	..	I	....	....	....	7	P.p.	Spontaneous labor at term	L	L	Albuminuria
278a	341	Velde and Volkmann, 1898	21	..	I	Yes	....	....	*	.....	.....	L	..	*Attack began in third trimester of pregnancy
b	342	Velde and Volkmann, 1898	23	..	II	Yes	....	....	2	P.p. on seventh day	Spontaneous labor at term	L	L	Chorea worse just before delivery
279	343	Ashworth, 1898	27	M	..	No	No	No	7	Until death	Induced premature labor	D	L	No albuminuria; no fever; anemia; death four and a half hours post partum
280	344	Delage, 1898	19	..	I	Yes	Yes	?	2	A.p. in eighth month	Spontaneous labor at term	L	L	Fright preceded attack
281	345	Delage, 1898	21	M	I	Yes	....	....	4	A.p. in seventh month	Spontaneous labor at term	L	L	Emotional disturbance preceded attack; second pregnancy normal
282	346	Delage, 1898	27	M	I	Yes	....	No	1	P.p.*	Spontaneous labor at term	L	L	*Chorea continued post partum, as long as patient was under observation
283a	347	Delage, 1898	20	..	I	Yes	Yes	....	1	P.p.	Spontaneous labor at term	L	L	
b	348	Delage, 1898	21	..	II	Yes	Yes	....	1	P.p.	Spontaneous labor at term	L	L	
c	349	Delage, 1898	24	..	III	Yes	Yes	....	1	2 days p.p.	Spontaneous labor at term	L	L	No albuminuria
284	350	Delage, 1898 (Duchemin)	18	..	I	Yes	....	....	3	.....	Spontaneous labor at term	L	L	
285	351	Delage, 1898 (Bernheim)	20	..	I	....	....	....	7	.....	.....	..	..	
286	352	Delage, 1898 (Bernheim)	19	..	I	Yes	....	....	.	.....	Spontaneous labor at term	L	L	
287	353	Delage, 1898 (Rontey)	21	..	I	Yes	....	....	4	.....	Spontaneous labor at term	L	L	
288	354	Delage, 1898 (Thoyer)	27	..	I	....	....	....	.	.....	Spontaneous labor at term	L	L	
289	355	Hartwig, 1898	19	..	..	Yes	....	No	6	A.p. in eighth month	.....	L	..	

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
290	356	Schrock, 1898	23	..	II	....	....	....	8	2 weeks p.p.	Spontaneous premature labor in seventh month	L	D	First pregnancy normal
291	357	Heymann, 1899	..	..	..	....	....	....	.	.....	Induced premature labor in seventh month	L	D	
292	358	Mastier, 1899	17	M	I	No	No	No	1	A.p. in third month	Spontaneous labor at term	L	L	
293	359	Gilles de la Tourette, 1899	17	..	II	....	....	....	.	.....	.....	..	..	Albuminuria; chorea complicated by mania
294	360	Gilles de la Tourette, 1899	..	..	II	Yes	Yes	....	2	.....	.....	..	..	
295	361	Piana, 1899	20	..	I	Yes	....	....	5	10 days p.p.	Induced abortion in fifth month	L	D	
296	362	Piana, 1899	23	M	I	....	....	Yes	1	Until death	Induced abortion in fourth month	D	D	Autopsy: negative except for vegetations on heart valves
297	363	Gentin, 1899	..	..	I	....	....	....	7	A.p. in ninth month	Spontaneous labor at term	L	D	Two subsequent pregnancies normal
298	364	Gentin, 1899	22	..	I	....	....	....	1	A.p.	Spontaneous labor at term	L	L	
299	365	Gentin, 1899	21	..	I	Yes	....	....	5	A.p.	Spontaneous labor at term	L	..	Emotional disturbance preceded attack; fetus had spina bifida and hydrocephalus
300	366	Gentin, 1899	17	..	II	Yes	....	....	.	A.p.	Spontaneous labor at term	L	L	No albuminuria
301	367	Gentin, 1899	20	..	I	Yes	....	....	1	A.p. in second month	Spontaneous labor at term	L	L	
302	368	Gentin, 1899	19	..	I	Yes	....	....	*	.....	Spontaneous labor at term	L	L	*Patient had had chorea continuously since her twelfth year
303	369	Gentin, 1899	17	..	I	Yes	....	....	1	.....	Spontaneous labor at term	L	..	
304	370	Gentin, 1899	..	..	I	....	....	....	.	.....	.....	L	..	Second pregnancy normal
305	371	Gentin, 1899	..	..	I	Yes	Yes	....	.	.....	.....	L	..	Fetus had spina bifida, clubfeet and hydrocephalus; second pregnancy normal
306	372	Gentin, 1899	18	..	III	Yes	....	....	.	A.p.	.....	L	D	Baby died of pemphigus on ninth day
307	373	Gentin, 1899	18	..	II	Yes	....	....	.	A.p.	Spontaneous labor at term	L	L	First pregnancy normal

306	372	Gentin, 1899	18	..	III	Yes	....	....	.	A.p.	.....	L	D	Baby died of pemphigus on ninth day
307	373	Gentin, 1899	18	..	II	Yes	....	....	.	A.p.	Spontaneous labor at term	L	L	First pregnancy normal
308	374	Gentin, 1899	..	..	II	Yes	....	....	1	P.p.	Spontaneous labor at term	L	L	First and third pregnancies normal
309a	375	Gentin, 1899	..	..	I	....	....	....	5	.....	.....	L	..	
b	376	Gentin, 1899	21	..	II	....	....	....	1	A.p. in ninth month	Spontaneous labor at term	L	L	
310a	377	Gentin, 1899	..	..	I	Yes	....	....	2	P.p.	.....	L	..	
b	378	Gentin, 1899	22	..	II	Yes	....	....	2	.....	Spontaneous labor at term	L	..	
311	379	Donat, 1899	25	M	II	Yes	....	....	4	6 weeks p.p.	Induced abortion in fifth month	L	D	First attack of chorea developed three weeks after first labor
312	380	Backhaus, 1899	21	..	I	No	No	Yes	6	Until death	Induced premature labor in ninth month	D	L	Autopsy: congestion of brain and meninges, recent endocarditis, bronchial pneumonia, cloudy swelling of liver, kidneys and heart
313	381	Reinhold, 1899	20	S	I	....	Yes	Yes	1	Until death	Died undelivered	D	D	Rheumatism with the chorea; autopsy: thrombosis of several cerebral sinuses, recent endocarditis
314	382	Wollenberg, 1899	24	..	IV	No	....	....	9	Until death	.....	D	..	First three pregnancies normal; death on fourteenth day post partum; autopsy: congestion of brain, endocarditis, pyelonephritis
315a	383	Wollenberg, 1899	..	..	II	....	....	....	.	.....	.....	L	..	
b	384	Wollenberg, 1899	25	..	III	Yes	....	....	3	P.p.	.....	L	D	
316a	385	Loviot, 1899	..	M	I	Yes	....	....	.	Several months p.p.	Spontaneous labor at term	L	..	
b	386	Loviot, 1899	..	M	II	Yes	....	....	1	4 days p.p.	Induced abortion	L	D	
317	387	Cardarelli, 1900	18	M	I	No	....	....	2	.....	.....	..	..	Fright preceded attack
318	388	Merttens, 1900	23	..	III	....	....	....	5	P.p.	Induced abortion in fifth month	L	D	
319	389	Oui, 1900	17	S	..	....	Yes	No	1	A.p. in third month	Spontaneous labor at term	L	L	Violent emotional disturbance with the chorea
320	390	Campione, 1900	31	M	IV	Yes	....	....	*	*	Induced premature labor	L	L	*Chorea present in chronic form when pregnancy began and continued post partum
321	391	Litten, 1900	20	S	..	....	....	Yes	*	Until death	Died undelivered in third month	D	D	*Onset of chorea prior to third month; autopsy: recent endocarditis and mitral insufficiency
322a	392	Gallion, 1900	26	M	I	Yes	....	....	.	P.p.*	Spontaneous premature labor in seventh month	L	D	*Chorea persisted slightly post partum; albuminuria
b	393	Gallion, 1900	..	M	II	Yes	....	....	5	P.p.	Spontaneous premature labor in eighth month	L	D	
323	394	Black, 1900	19	M	II	No	No	?	5	P.p.	Induced premature labor	L	L	Mania with the chorea
324a	395	Black, 1900	..	M	II	Yes	*	?	7	3 hours p.p.	Spontaneous labor at term	L	..	*First pregnancy normal; rheumatism between first and second pregnancies
b	396	Black, 1900	25	M	III	Yes	Yes	Yes	6	5 days p.p.	Induced premature labor	L	L	Fright preceded attack
325	397	Meade, 1901	25	M	..	....	....	....	.	A.p.	.....	L	..	
326	398	Purefoy, Lloyd and Carton, 1901	21	..	I	Yes	....	....	.	P.p.	Spontaneous labor at term	L	L	Baby had chorea at birth, but recovered rapidly
327	399	Purefoy, Lloyd and Carton, 1901	23	..	I	....	....	....	.	P.p.	Spontaneous labor at term	L	D	
328	400	Purefoy, Lloyd and Carton, 1901	24	..	I	Yes	....	....	.	P.p.	Spontaneous labor at term	L	L	

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea¶	Fate of the Pregnancy	Result for Mother#	Result for Child**	Comment
329	401	Jolly, 1901	..	..	..	....	....	....	7	Until death	Spontaneous premature labor	D	..	Death a few days post partum
330	402	Hennig, 1901	25	M	II	No	....	No	6	P.p.	Spontaneous labor at term	L	D	First pregnancy normal
331	403	Routh, 1901	..	M	I	No	No	....	4	A.p. in sixth month	.....	..	..	
332	404	Routh, 1901 (Pollock)	20	S	..	....	No	No	.	P.p.	Induced abortion	L	D	Patient kept under chloroform by relays of students; puerperal psychosis
333	405	Newell, 1901	19	..	I	Yes	....	[illegible]	2	A.p. in eighth month	Spontaneous labor at term	L	..	
334	406	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
335	407	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
336	408	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
337	409	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
338	410	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
339	411	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
340	412	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
341	413	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
342	414	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
343	415	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
344	416	Newell, 1901	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
345	417	Newell, 1901	..	..	III	No	....	....	.	P.p.	.....	L	..	First two pregnancies normal
346	418	Newell, 1901	..	..	II	Yes	....	....	.	P.p.	.....	L	..	First pregnancy normal
347	419	Kruger, 1902	20	..	I	No	No	....	4	8 days p.p.	Induced premature labor in seventh month	L	D	
348	420	Kruger, 1902	18	..	II	....	....	....	2	9 days p.p.	Induced abortion in third month	L	D	
349	421	Menzel, 1902	21	M	I	....	No	No	2	P.p.	Spontaneous labor at term	L	L	
350	422	Bumm, 1902	21	..	I	....	....	....	3	8 days p.p.	Vaginal hysterotomy	L	D	
351a	423	Jones, 1903	21	S	..	....	....	.....	5	.....	Spontaneous labor at term	L	D	Stillbirth; mania preceded onset of the chorea
b	424	Jones, 1903	21	S	..	Yes	....	.....	6	*	Spontaneous premature labor	L	..	*Chorea persisting three months post partum; mania in this pregnancy also

b	424	Jones, 1903	23	S	..	Yes	....	....	6	*	Spontaneous premature labor	L	..	*Chorea persisting three months post partum; mania in this pregnancy also
352	425	Copeman, 1903	28	M	III	No	No	No	3	A.p. in fourth month	.....	L	..	Tonsillitis preceded the attack, which cleared up following removal of urethral caruncle
353	426	Hellier, 1903	23	M	II	No	Yes	?	3	6 weeks p.p.	Spontaneous labor at term	L	D	Stillbirth; mania preceded onset of the chorea
354	427	Hart, 1903	18	M	II	No	No	....	2	3 weeks p.p.	Induced abortion in second month	L	D	Fright preceded attack; some mental disturbance; first pregnancy normal
355	428	Hart, 1903	19	M	..	....	....	....	.	A.p.	.....	L	..	
356	429	Wall and Andrews, 1903	21	M	I	No	Yes	No	4	A.p. in sixth month	.....	L	..	
357	430	Wall and Andrews, 1903	20	M	II	Yes	No	No	6	6 weeks p.p.	Induced abortion in sixth month	L	D	Fright preceded attack
358	431	Wall and Andrews, 1903	19	M	I	Yes	Yes	No	3	A.p. in fourth month	.....	L	..	
359	432	Wall and Andrews, 1903	22	M	III	Yes	No	No	4	A.p. in seventh month	.....	L	..	
360	433	Wall and Andrews, 1903	28	M	I	Yes	Yes	Yes	5	A.p. in seventh month	.....	L	..	
361	434	Wall and Andrews, 1903	23	M	III	No	No	No	6	10 days p.p.	Spontaneous labor at term	L	L	First two pregnancies normal
362	435	Wall and Andrews, 1903	24	M	I	Yes	No	No	3	A.p. in fifth month	.....	L	..	Fright preceded attack
363	436	Wall and Andrews, 1903	22	M	I	Yes	No	No	2	A.p. in third month	.....	L	..	
364	437	Wall and Andrews, 1903	20	M	I	Yes	No	No	2	.....	.....	L	..	
365	438	Wall and Andrews, 1903	18	S	I	No	No	Yes	5	A.p. in fifth month	.....	L	..	Fright preceded attack; slight albuminuria
366	439	Wall and Andrews, 1903	33	M	VII	No	No	No	4	.....	.....	L	..	Fright preceded the attack
367	440	Wall and Andrews, 1903	22	M	II	Yes	No	Yes	6	.....	.....	L	..	Fright preceded the attack; first pregnancy normal
368	441	Wall and Andrews, 1903	27	M	I	Yes	No	Yes	5	.....	.....	L	..	
369	442	Wall and Andrews, 1903	20	M	I	Yes	Yes	No	*	"	Induced abortion	L	D	*Onset of chorea preceded the pregnancy by one month; improvement following the abortion, but the chorea continued; chorea complicated by acute rheumatism
370	443	Wall and Andrews, 1903	19	S	I	No	No	No	6	.....	.....	L	..	
371	444	Wall and Andrews, 1903	21	S	I	Yes	No	Yes	2	.....	.....	L	..	
372	445	Wall and Andrews, 1903	22	M	I	Yes	No	No	6	A.p. in seventh month	.....	L	..	
373	446	Wall and Andrews, 1903	22	M	II	Yes	No	No	6	.....	.....	L	..	
374	447	Wall and Andrews, 1903	26	M	III	Yes	No	No	8	.....	Spontaneous labor at term	L	L	
375	448	Wall and Andrews, 1903	19	S	I	Yes	Yes	No	5	.....	.....	L	..	
376	449	Wall and Andrews, 1903	25	M	II	No	Yes	Yes	4	A.p. in seventh month	.....	L	..	Patient much worried before attack of chorea
377	450	Wall and Andrews, 1903	18	M	I	No	No	No	3	.....	.....	L	..	Emotional disturbance preceded the onset of the chorea
378	451	Wall and Andrews, 1903	21	M	I	No	No	No	3	.....	.....	L	..	Patient was syphilitic
379	452	Wall and Andrews, 1903	22	S	I	Yes	No	No	7	7 weeks p.p.	Spontaneous premature labor in seventh month	L	D	Stillbirth; patient much worried before the attack of chorea
380	453	Wall and Andrews, 1903	23	M	III	No	Yes	....	2	.....	Spontaneous rupture of ectopic pregnancy	L	D	

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
381	454	Wall and Andrews, 1903	21	M	II	Yes	No	Yes	5	1 month p.p.	Spontaneous premature labor in seventh month	L	L	First pregnancy normal
382	455	Wall and Andrews, 1903	22	M	II	Yes	No	No	4	.....	Spontaneous labor at term	L	L	
383	456	Wall and Andrews, 1903	22	M	I	Yes	No	....	7	4 weeks p.p.	Spontaneous labor at term	L	L	
384	457	Wall and Andrews, 1903	21	S	I	No	No	No	5	.....	.....	..	..	Patient worried before attack
385	458	Wall and Andrews, 1903	22	M	III	Yes	Yes	Yes	.	A.p.	.....	L	..	
386	459	Wall and Andrews, 1903	21	M	I	....	Yes	No	.	Until death	Induced abortion	D	D	Autopsy: infected clot in uterus, endocarditis
387	460	Wall and Andrews, 1903	21	M	I	Yes	No	Yes	5	Until death	Induced abortion	D	D	Autopsy: edema of lungs and endocarditis
388	461	Wall and Andrews, 1903	28	M	V	No	No	No	5	Until death	Induced abortion	D	D	Chorea treated with chloroform inhalations; first four pregnancies normal
389	462	Wall and Andrews, 1903	23	M	IV	Yes	No	Yes	3	Until death	Died undelivered	D	D	First three pregnancies normal; patient worried before attack; mania
390	463	Wall and Andrews, 1903	21	M	I	No	No	Yes	1	Until death	Induced abortion	D	D	Autopsy: embolism in spleen, kidneys and left middle cerebral artery
391a	464	Wall and Andrews, 1903	21	M	I	Yes	No	No	4	.....	Spontaneous labor at term	L	L	
b	465	Wall and Andrews, 1903	26	M	III	Yes	No	No	8	5 weeks p.p.	Spontaneous labor at term	L	L	Second pregnancy free from chorea
392a	466	Wall and Andrews, 1903	..	M	I	Yes	No	....	.	.....	.....	L	..	
b	467	Wall and Andrews, 1903	25	M	II	Yes	No	Yes	3	4 weeks p.p.	Spontaneous premature labor in seventh month	L	L	
393a	468	Wall and Andrews, 1903	22	M	I	No	No	....	.	.....	.....	L	..	
b	469	Wall and Andrews, 1903	23	M	II	Yes	No	....	.	.....	.....	L	..	
c	470	Wall and Andrews, 1903	23	M	III	Yes	No	No	2	.....	.....	L	..	
394a	471	Wall and Andrews, 1903	15	M	I	No	Yes	....	.	.....	.....	L	..	
b	472	Wall and Andrews, 1903	29	M	XIII	Yes	Yes	....	4	3 weeks p.p.	Spontaneous premature labor in eighth month	L	L	Chorea in first and thirteenth pregnancies; seven pregnancies ended in miscarriage
395a	473	Rozenblum, 1903	24	M	II	Yes	No	....	1	P.p.	Induced abortion	L	D	First attack of chorea began two weeks after first labor
b	474	Rozenblum, 1903	..	M	III	Yes	No	....	1	P.p.	Spontaneous labor at term	L	L	

b	474	Rozenblum, 1903	..	M	III	Yes	No	....	1	P.p.	Spontaneous labor at term	L	L	weeks after first labor
396	475	Duckworth, 1903	24	M	VIII	....	Yes	Yes	5	P.p.	Spontaneous abortion*	L	D	*Abortion began spontaneously, but was terminated surgically; fright preceded attack; mania; no albuminuria
397	476	Duckworth, 1903	..	M	*	Yes	No	Yes	5	.....	.....	L	..	*Multipara; fright preceded attack
398	477	Hirschl, 1903	20	S	..	....	....	No	8	9 days p.p.	Spontaneous premature labor in eighth month	L	L	Fright preceded attack; two attacks of mania
399	478	Dentler, 1903	32	..	III	....	....	Yes	8	Until death	Induced premature labor	D	..	Autopsy; recent endocarditis, purulent leptomeningitis, puerperal sepsis
400	479	Siemerling, 1904	..	..	..	....	....	....	.	.....	.....	D	..	
401	480	Siemerling, 1904	..	..	..	....	....	....	.	.....	.....	D	..	
402	481	Siemerling, 1904	..	..	..	....	....	....	.	.....	.....	D	..	
403	482	Siemerling, 1904	..	..	..	Yes	....	....	*	.....	.....	L	..	*Chorea for ten years before pregnancy, became worse during pregnancy and improved post partum
404	483	Vallois, 1904	26	..	I	....	....	....	6	1 week p.p.	Spontaneous premature labor in eighth month	L	L	Psychosis antedated the chorea and persisted post partum; albuminuria
405	484	Loquifer, 1904	25	..	III	No	....	....	4	A.p. in sixth month	Spontaneous labor at term	L	L	
406	485	Lequyer, 1904	26	..	I	No	No	No	5	P.p.	Spontaneous premature labor in eighth month	L	L	Fright preceded attack; puerperal psychosis; albuminuria
407	486	Shoemaker, 1904	17	S	..	....	Yes	....	.	.....	.....	..	..	
408	487	Semple, 1904	24	M	I	No	No	....	3	Until death	Induced abortion in third month	D	D	Albuminuria
409	488	Semple, 1904	18	M	I	No	Yes	?	1	P.p.	Induced abortion in second month	L	D	*Acute rheumatism before beginning of pregnancy; albuminuria
410	489	Koritkowski, 1904	18	M	I	....	....	Yes	3	Until death	Induced abortion in fifth month	D	D	Autopsy: recent endocarditis, pyelitis, cystitis, metritis, bronchial pneumonia and hyperemia cerebri
411	490	Koritkowski, 1904	18	S	I	....	....	....	5	P.p.	Induced abortion in fifth month	L	D	
412a	491	Koritkowski, 1904	26	M	II	....	No	....	9	4 days p.p.	Spontaneous labor at term	L	L	First pregnancy normal
b	492	Koritkowski, 1904	28	M	III	Yes	No	....	5	4 days p.p.	Spontaneous labor at term	L	L	
c	493	Koritkowski, 1904	30	M	IV	Yes	No	?	7	9 days p.p.	Spontaneous labor at term	L	L	
413	494	Koritkowski, 1904 (Abrahams)	28	..	..	....	....	....	.	Until death	.....	D	..	
414	495	Pelnář, 1904	..	..	..	....	....	Yes	.	.....	.....	D	..	Autopsy; congestion of brain, parenchymatous degeneration of various organs and endocarditis; see text
415	496	Frank, 1904	21	M	II	....	No	No	2	P.p.	Spontaneous labor at term	L	L	First pregnancy normal; albuminuria
416	497	Seiler, 1905	22	M	I	Yes	....	....	3	1 year p.p.	Spontaneous labor at term	L	L	
417	498	Seiler, 1905	26	M	I	....	....	....	5	Until death	Died undelivered in sixth month*	D	D	*Death following convulsions and coma twenty-four hours after attempted induction of abortion under chloroform narcosis
418	499	Dixon, 1905	22	M	I	....	Yes	?	6	6 weeks p.p.	Spontaneous labor at term	L	L	Mania

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
419	500	Gould and Howell, 1905	19	..	I	....	No	?	8	A.p. in ninth month	Induced labor at term*	L	L	*Patient had eclampsia after recovery from chorea, and labor was induced for this indication; fright preceded attack
420	501	Gettkant, 1905	19	..	I	....	Yes	No	4	P.p.	Induced premature labor in eighth month	L	L	
421	502	Gettkant, 1905	18	..	I	Yes	No	....	*	P.p.	Spontaneous labor at term	L	L	*Onset of chorea early in pregnancy
422	503	Gettkant, 1905	19	M	II	....	....	?	2	P.p.	Induced premature labor in eighth month	L	L	First pregnancy normal
423a	504	Gettkant, 1905	19	..	I	No	No	No	3	P.p.	Induced abortion in sixth month	L	D	
b	505	Gettkant, 1905	20	M	II	Yes	No	....	7	P.p.	Induced premature labor in eighth month	L	D	
424	506	Kouwer, 1906	..	..	IV	....	....	....	.	P.p.	Spontaneous premature labor in eighth month	L	..	First three pregnancies normal; anemia
425	507	Sheill, 1906	..	M	I	No	No	No	*	P.p.	Spontaneous labor at term	L	..	*Onset of chorea in middle of pregnancy
426a	508	Sheill, 1906	20	M	II	No	No	No	8	P.p.	Spontaneous labor at term	L	L	First pregnancy normal
b	509	Sheill, 1906	23	M	III	Yes	No	....	5	Until death	Induced abortion in sixth month	D	D	Mania; chloroform inhalations to control chorea
427	510	French and Hicks, 1906	24	M	I	No	No	No	4	A.p. in seventh month	Spontaneous labor at term	L	..	Albuminuria
428	511	French and Hicks, 1906	19	S	I	....	Yes	Yes	7	A.p. in eighth month	.....	L	..	
429	512	French and Hicks, 1906	20	M	I	Yes	....	....	1	Rapid recovery a.p.	.....	L	..	Fright preceded attack
430	513	French and Hicks, 1906	20	M	I	No	No	....	4	Rapid recovery a.p.	.....	L	..	
431	514	French and Hicks, 1906	22	M	III	No	No	No	1	A.p. in third month	.....	L	..	First two pregnancies normal
432	515	French and Hicks, 1906	22	M	I	Yes	....	?	3	A.p. in fifth month	.....	L	..	
433	516	French and Hicks, 1906	27	M	III	No	No	Yes	7	A.p. in eighth month	.....	L	..	First two pregnancies normal

433	515	French and Hicks, 1906	22	M	I	Yes	....	?	3	A.p. in fifth month	.....	L	..	
434	516	French and Hicks, 1906	27	M	III	No	No	Yes	7	A.p. in eighth month	.....	L	..	First two pregnancies normal
434	517	French and Hicks, 1906	21	S	..	No	No	No	4	A.p. in sixth month	.....	L	..	
435	518	French and Hicks, 1906	23	M	III	....	Yes	No	4	Rapid recovery a.p.	.....	L	..	First two pregnancies normal
436	519	French and Hicks, 1906	20	M	I	Yes	....	?	2	A.p. in fourth month	.....	L	..	
437	520	French and Hicks, 1906	31	M	I	Yes	....	No	7	A.p.	Spontaneous labor at term	L	..	
438	521	French and Hicks, 1906	21	M	I	Yes	....	....	6	P.p.	Spontaneous labor at term	L	L	
439	522	French and Hicks, 1906	17	M	I	Yes	Yes	?	3	A.p. in sixth month	.....	L	..	Fright preceded attack
440	523	French and Hicks, 1906	20	M	I	No	No	No	1	A.p. in third month	.....	L	..	
441	524	French and Hicks, 1906	27	S	..	Yes	Yes	Yes	3	A.p. in sixth month	.....	L	..	
442	525	French and Hicks, 1906	20	M	I	Yes	No	....	5	*	Induced premature labor in seventh month	L	..	*Chorea was still present two months post partum
443	526	French and Hicks, 1906	21	S	I	No	No	....	2	A.p. in fifth month	.....	L	..	
444	527	French and Hicks, 1906	30	M	II	Yes	No	No	7	2 weeks p.p.	Spontaneous premature labor in seventh month*	L	D	First pregnancy normal, although chorea antedated it; *stillbirth
445	528	French and Hicks, 1906	22	M	III	No	No	No	4	.....	.....	L	..	Patient worried before attack; first two pregnancies normal
446	529	French and Hicks, 1906	30	M	II	Yes	Yes	....	2	.....	.....	L	..	First pregnancy normal; chorea complicated by acute rheumatism
447	530	French and Hicks, 1906	20	M	I	Yes	....	....	*	*	.....	..	..	*Chorea present when pregnancy began and still present when patient passed from observation
448	531	French and Hicks, 1906	26	M	I	Yes	....	Yes	6	.....	Spontaneous labor at term	L	L	
449	532	French and Hicks, 1906	21	M	I	Yes	....	Yes	3	Until death	Spontaneous abortion in fourth month	D	D	Autopsy; recent endocarditis and parotitis; cultures from spleen, heart's blood and cerebrospinal fluid all sterile
450	533	French and Hicks, 1906	21	M	I	No	No	Yes	1	Until death	Curettage in second month	D	D	Chloroform inhalations to control chorea; death on fifth day post partum; for autopsy see text
451	534	French and Hicks, 1906	23	M	IV	No	No	Yes	5	Until death	Spontaneous premature labor in seventh month	D	D	First three pregnancies normal; three weeks before death patient had a convulsion followed by coma and hemiplegia; autopsy; recent endocarditis
452a	535	French and Hicks, 1906	..	M	I	Yes	No	No	5	1 month p.p.	.....	L	..	
b	536	French and Hicks, 1906	25	M	V	Yes	No	No	5	P.p.	Spontaneous labor at term	L	L	Second, third and fourth pregnancies free from chorea
453a	537	French and Hicks, 1906	..	M	I	No	No	N..	2	A.p. in third month	Spontaneous labor at term	L	L	
b	538	French and Hicks, 1906	23	M	II	Yes	No	No	2	A.p. in third month	.....	L	..	
454a	539	French and Hicks, 1906	16	M	I	Yes	Yes	....	*	1 month p.p.	Spontaneous premature labor in eighth month*	L	D	*Chorea present before pregnancy began; stillbirth

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea¶	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
b	540	French and Hicks, 1906	..	M	II	Yes	Yes	....	2	1 month p.p.	Spontaneous abortion in fifth month	L	D	
c	541	French and Hicks, 1906	25	M	III	Yes	Yes	....	2	*	Spontaneous premature labor in seventh month	L	D	*Fetus died in sixth month, but pregnancy continued to seventh month with only slight improvement of chorea, which was still present when patient was discharged
455a	542	French and Hicks, 1906	*	M	I	No	No	....	.	P.p.	Spontaneous labor at term	L	L	*Patient under 20 years of age; fright preceded attack
b	543	French and Hicks, 1906	20	M	II	Yes	No	....	1	P.p.	Spontaneous labor at term	L	L	
456a	544	Martin, 1906	23	M	I	Yes	Yes	....	*	*	Spontaneous labor at term	L	..	*Chorea was present when pregnancy began and continued post partum
b	545	Martin, 1906	..	M	II	Yes	Yes	....	*	*	Spontaneous labor at term	L	..	*Chorea was present when pregnancy began and continued post partum
c	546	Martin, 1906	..	M	III	Yes	Yes	Yes	*	*	Induced abortion in sixth month	L	D	*Chorea was present when pregnancy began and continued post partum
d	547	Martin, 1906	..	M	IV	Yes	Yes	Yes	*	*	Spontaneous labor at term	L	L	*Chorea was present when pregnancy began and continued post partum
457	548	Poynton and Holmes 1906	16	..	I	Yes	Yes	....	.	.....	.....	L	..	
458	549	Templeton, 1906	23	..	II	....	....	....	2	P.p.	Pregnancy interrupted artificially*	L	..	*Month not given
459	550	Dubrandy, 1906	23	M	I	....	....	....	5	A.p. in seventh month	Spontaneous labor at term	L	L	Emotional disturbance before onset of chorea; second pregnancy normal
460	551	Mussellwhite, 1907	19	S	I	....	....	....	.	P.p.	Spontaneous premature labor	L	D	Mania for two weeks; no chorea in two subsequent pregnancies
461a	552	Foulkrod, 1907	..	M	I	Yes	....	....	.	P.p.	Induced premature labor in eighth month	L	D	Eclampsia
b	553	Foulkrod, 1907	..	M	II	Yes	....	....	.	P.p.	Spontaneous abortion in fourth month	L	D	
c	554	Foulkrod, 1907	..	M	III	Yes	....	....	.	P.p.	Spontaneous abortion in third month	L	D	

d	555	Foulkrod, 1907	..	M	IV	Yes	....	....	.	P.p.	Spontaneous abortion in third month	L	D	
e	556	Foulkrod, 1907	25	M	V	Yes	....	....	.	.....	Spontaneous labor at term	L	L	Rest, chloral and bromides
462	557	Frigyesi, 1907	23	..	II	....	....	Yes	5	Until death	Induced abortion in fifth month	D	D	Autopsy: congestion of brain and acute endocarditis
463	558	Goldberger, 1907	30	..	II	....	....	....	2	Until death	Induced abortion	D	D	
464	559	Meyer, 1907	36	M	IV	No	No	....	4	A.p. in fourth month	Spontaneous labor at term	L	L	Fright preceded attack; two subsequent pregnancies normal
465	560	Meyer, 1907	25	..	I	No	No	No	7	2 weeks p.p.	Spontaneous labor at term	L	L	Emotional disturbance preceded onset of chorea
466	561	Meyer, 1907	20	..	I	Yes	Yes	Yes	.	A.p.	.....	L	..	Albuminuria
467a	562	Meyer, 1907	20	M	I	Yes	No	....	*	1 day p.p.	Spontaneous labor at term	L	L	*Onset of chorea in middle third of pregnancy
b	563	Meyer, 1907	21	M	II	Yes	No	No	*	.....	.....	..	..	*Onset of chorea in second half of pregnancy
468	564	Meyer, 1907 (Lloyd)	26	..	III	Yes	Yes	....	1	P.p.	.....	L	..	
469	565	Shaw, 1907	25	..	I	No	No	....	9	Until death	Spontaneous labor at term*	D	D	Fright preceded attack; *labor terminated by accouchement forcé
470	566	Shaw, 1907	18	*	I	No	No	*	.	2 weeks p.p.	Induced premature labor in seventh month	D	D	*Patient worried by forced marriage during pregnancy; death one month post partum from acute endocarditis
471	567	Shaw, 1907	30	..	I	No	No	No	5	A.p. in seventh month	Spontaneous premature labor in seventh month	L	L	Fright preceded attack
472	568	Shaw, 1907	25	..	I	Yes	....	No	3	A.p. in fifth month	Spontaneous labor at term	L	D	Fetal death not due to chorea; stillbirth
473	569	Shaw, 1907	21	S	I	....	....	....	8	1 month p.p.	Spontaneous labor at term	L	L	Mania; chorea became much worse after labor
474	570	Shaw, 1907	19	..	I	No	No	No	2	A.p. in sixth month	.....	L	..	Emotional disturbance preceded attack
475	571	Shaw, 1907	21	..	I	Yes	Yes	....	6	A.p. in eighth month	Spontaneous labor at term	L	L	
476	572	Shaw, 1907	27	..	I	Yes	....	....	7	3 weeks p.p.	Spontaneous labor at term	L	..	
477	573	Shaw, 1907	23	..	I	No	No	....	6	20 days p.p.	Spontaneous labor at term	L	D	Fetal death fourteen days post partum, probably not due to chorea
478	574	Shaw, 1907	33	..	III	....	....	....	5	A.p. in seventh month	.....	L	..	
479a	575	Shaw, 1907	20	..	I	....	....	....	.	.....	.....	L	..	
b	576	Shaw, 1907	21	..	II	Yes	....	....	.	3 weeks p.p.	Spontaneous labor at term	L	L	
480a	577	Wallace, 1907	18	..	I	Yes	....	....	9	4 days p.p.	Spontaneous labor at term	L	D	Baby had hydrocephalus
b	578	Wallace, 1907	22	..	II	Yes	....	....	8	10 days p.p.	Spontaneous labor at term	L	D	
481	579	Gress, 1907	22	S	I	....	No	No	5	P.p.	Spontaneous premature labor in ninth month	L	L	
482	580	Robertson, 1908	28	M	I	No	No	....	2	*	Spontaneous abortion in fifth month	L	D	*Chorea still present eighteen months post partum

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
483	581	Robertson, 1908	..	M	..	No	....	....	1	P.p.	Induced abortion in second month	L	D	
484	582	Shaw, 1908	18	S	I	Yes	....	....	4	A.p. in seventh month	Spontaneous labor at term	L	L	
485	583	Shaw, 1908	21	*	I	No	No	....	4	10 days p.p.	Spontaneous abortion in fifth month	L	D	*Married during pregnancy; abortion attributed to pneumonia
486	584	Shaw, 1908	23	M	I	Yes	....	....	5	A.p. in eighth month	Spontaneous labor at term	L	L	
487	585	Quensel, 1908	..	..	..	....	....	....	.	A.p.	.....	L	..	
488	586	Quensel, 1908	..	..	..	....	....	....	.	A.p.	.....	L	..	
489	587	Quensel, 1908	..	..	..	....	....	....	.	.....	Accouchement forcé	D	..	
490	588	Quensel, 1908	..	..	..	....	....	....	.	.....	Accouchement forcé	D	..	
491	589	Quensel, 1908	..	..	..	....	....	....	.	.....	Spontaneous abortion	D	D	
492	590	Hakkebouche and Gostchik, 1908	21	..	II	....	....	....	7	.....	Induced abortion	L	D	
493	591	Birnbaum, 1910	18	*	I	No	....	No	2	Until death	Induced abortion in fifth month	D	D	*Patient married during pregnancy; death forty-eight hours post partum; autopsy negative; bacteriologic examinations of blood and brain were negative
494	592	Viedenz, 1910	21	M	II	No	....	....	2	P.p.*	Spontaneous abortion	L	D	First pregnancy normal; *chorea continued for eighteen months post partum
495	593	Runge, 1910	25	M	V	No	....	Yes	5	1 week p.p.	Spontaneous labor at term	L	L	
496	594	Runge, 1910	24	M	IV	....	....	....	3	3 months p.p.	Spontaneous premature labor in eighth month	L	D	No chorea in other pregnancies
497	595	Runge, 1910	20	M	II	No	....	....	3	Until death	Died undelivered in fourth month	D	D	High fever; pulse rate, 160
498	596	Croft, 1910	..	..	..	....	*	Yes	.	Over 3 months p.p.	Spontaneous abortion	L	D	*Rheumatism complicated the chorea
499	597	Croft, 1910	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	L	Severe attack associated with mental disturbance
500	598	Croft, 1910	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	L	Severe attack associated with mental disturbance

599	598	Croft, 1910	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	L	Severe attack associated with mental disturbance
501	599	Croft, 1910	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	L	Severe attack associated with mental disturbance
502	600	Croft, 1910	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	L	Severe attack associated with mental disturbance
503	601	Croft, 1910	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	L	Severe attack associated with mental disturbance
504	602	Croft, 1910	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	L	
505	603	Croft, 1910	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	L	
506	604	Croft, 1910	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	L	
507a	605	Croft, 1910	..	..	II	....	....	....	.	P.p.	Induced abortion in sixth month	L	D	
b	606	Croft, 1910	..	..	VI	Yes	....	....	.	.....	Spontaneous labor at term	L	..	
508	607	Villiapadierna, 1910	26	M	VI	....	No	Yes	.	Until death	Induced premature labor in eighth month	D	L	First five pregnancies normal; autopsy: congestion of meninges and adhesions over motor area, old endocarditis
509	608	Diekman, 1911	..	..	..	Yes	....	....	.	.....	.....	L	..	
510	609	Diekman, 1911	..	..	..	Yes	....	No	.	Until death	Vaginal cesarean section	D	..	
511	610	Diekman, 1911	..	..	..	No	....	Yes	.	Until death	Vaginal cesarean section	D	..	
512	611	Diekman, 1911 (Courant)	..	..	..	....	....	....	.	Until death	Spontaneous abortion in sixth month	D	D	Patient died ten days post partum; hypostatic pneumonia
513a	612	Diekman, 1911 (Hannes)	..	..	I	....	....	....	.	.....	.....	L	..	
b	613	Diekman, 1911 (Hannes)	..	..	II	Yes	....	....	.	.....	.....	L	..	
c	614	Diekman, 1911 (Hannes)	..	..	III	Yes	....	....	*	Until death	Total vaginal extirpation	D	D	*Chorea began in first trimester of pregnancy
514	615	Randle, 1912	26	M	IV	No	Yes	....	4	2 weeks p.p.	Induced abortion in fifth month	L	D	First three pregnancies normal; acute articular rheumatism since third pregnancy
515	616	Nicolauer, 1912	18	..	II	....	....	....	5	P.p.	Spontaneous labor at term	L	..	Psychosis with the chorea
516	617	Chotzen, 1912	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	..	
517	618	Chotzen, 1912	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	..	
518	619	Chotzen, 1912	..	..	..	....	....	....	.	.....	Pregnancy interrupted artificially*	D	..	*Month not given
519a	620	Chotzen, 1912	..	..	..	....	....	....	.	P.p.	Spontaneous labor at term	L	..	
b	621	Chotzen, 1912	..	..	*	Yes	....	....	.	P.p.	Induced interruption of pregnancy	L	..	*Multipara
520	622	Kramer, 1912	..	..	..	....	....	Yes	.	Until death	Pregnancy interrupted artificially*	D	..	*Month not given; autopsy: endocarditis and myocarditis
521	623	Kramer, 1912	..	..	..	Yes	....	....	.	A.p.	Spontaneous labor at term	L	..	
522	624	Kramer, 1912	..	..	..	....	....	....	.	A.p.*	Spontaneous labor at term	L	..	*Attack lasted eight weeks

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea¶	Fate of the Pregnancy	Result for Mother#	Result for Child**	Comment
523a	625	Kramer, 1912	..	..	..	....	....	....	.	.....	.....	L	..	
b	626	Kramer, 1912	..	M	*	Yes	....	Yes	.	Until death	Spontaneous interruption of pregnancy	D	..	*Multipara; autopsy: endocarditis and myocarditis
524a	627	Kramer, 1912	..	..	..	....	....	....	.	.....	.....	L	..	
b	628	Kramer, 1912	..	M	*	Yes	....	Yes	.	Until death	Induced interruption of pregnancy	D	..	*Multipara; autopsy: endocarditis and myocarditis
525	629	Meumann, 1912	21	..	I	Yes	Yes	No	.	P.p.	Spontaneous labor at term	L	L	No albuminuria
526	630	Meumann, 1912	18	S	I	Yes	Yes	Yes	.	P.p.	Spontaneous labor at term	L	L	No albuminuria
527	631	Meumann, 1912	19	M	I	....	....	....	.	.....	.....	..	..	
528	632	Meumann, 1912	23	M	I	....	....	....	6	Until death	.....	D	..	
529	633	Meumann, 1912	20	S	II	No	No	No	8	P.p.	Induced premature labor	L	L	Fright preceded the attack; no albuminuria; first pregnancy normal
530	634	Meumann, 1912	20	..	II	....	....	?	*	P.p.	Induced abortion in sixth month	L	D	*Onset of chorea before sixth month; complicated by hysterical hemiparesis; no albuminuria
531	635	Meumann, 1912	25	M	III	....	....	?	9	Until death	Induced labor at term	D	D	First two pregnancies normal; no albuminuria
532	636	Meumann, 1912	20	S	I	Yes	....	....	5	Until death	Induced abortion in sixth month	D	D	Albuminuria
533	637	Meumann, 1912	25	S	I	Yes	....	No	9	P.p.	Induced premature labor in ninth month	L	D	No albuminuria
534	638	Meumann, 1912	22	M	III	No	No	?	*	Until death	Induced abortion in sixth month	D	D	*Early onset; no albuminuria; death on second day post partum; first two pregnancies normal
535a	639	Meumann, 1912	27	..	I	Yes	Yes	....	.	P.p.	.....	L	..	
b	640	Meumann, 1912	28	..	II	Yes	Yes	....	6	9 days p.p.	Induced premature labor	L	D	Albuminuria
c	641	Meumann, 1912	31	..	IV	Yes	Yes	?	6	P.p.	Induced abortion in sixth month	L	D	Third pregnancy free from chorea; albuminuria
536a	642	Meumann, 1912	21	M	I	No	No	....	3	A.p. in fifth	Spontaneous labor at term	L	L	

c	641	Meumann, 1912	31	..	IV	Yes	Yes	?	6	P.p.	Induced abortion in sixth month	L	L	albuminuria
536a	642	Meumann, 1912	21	M	I	No	No	....	3	A.p. in fifth	Spontaneous labor at term	L	L	
b	643	Meumann, 1912	23	M	II	Yes	No	Yes	1	P.p.	Vaginal hysterotomy in fourth month	L	D	No albuminuria
537	644	Dobkevitch, 1913	25	M	II	....	....	....	2	1 day p.p.	Induced abortion in fourth month	D	D	Patient given 20 cc. of blood serum from normal pregnant woman; first pregnancy normal
538	645	Dobkevitch, 1913 (Ballantine)	25	M	I	Yes	....	....	3	Until death	Died undelivered	D	D	Onset of chorea followed the extraction of a tooth
539	646	Potocki and Sauvage, 1913	20	..	I	No	No	Yes	2	Until death	Died undelivered in third month*	D	D	*Death three weeks after onset of chorea and four hours after attempted abortion; no albuminuria; autopsy: recent severe endocarditis
540	647	Fraipont, 1913	29	M	I	No	....	....	5	3 days p.p.*	Spontaneous premature labor in ninth month	D	L	*Chorea improved at once after delivery, but mania and fever developed with no evidence of postpartum infection; no albuminuria; great anger preceding the onset of the attack
541	648	Fraipont, 1913	25	M	II	....	....	....	5	12 days p.p.	Spontaneous labor at term	L	L	Fright preceded the attack; no albuminuria; first pregnancy normal
542a	649	Fraipont, 1913	23	M	III	Yes	....	....	7	12 days p.p.	Spontaneous labor at term	L	L	First two pregnancies free from chorea
b	650	Fraipont, 1913	25	M	IV	Yes	....	....	1	10 days p.p.	Spontaneous labor at term	L	L	
543	651	Härtel	..	S	..	....	....	No	7	A.p. in eighth month	.....	L	..	Treated with arsphenamine; Wassermann reaction negative; no albuminuria
544	652	Wilson, 1913	23	..	..	....	No	No	5	Until death	Died undelivered in seventh month	D	D	Patient syphilitic; for autopsy see text
545	653	Hoff, 1913	26	..	..	....	Yes	....	5	.....	.....	..	..	
546	654	Hoff, 1913	23	M	..	....	....	?	2	.....	.....	..	..	
547	655	Hoff, 1913	24	M	..	....	....	....	7	P.p.	Spontaneous premature labor in seventh month	L	D	
548	656	Mühlbaum, 1913	24	S	..	Yes	Yes	?	*	1 month p.p.	Induced abortion	L	D	*Onset of chorea early in pregnancy
549a	657	Mühlbaum, 1913	21	M	I	....	....	....	6	8 weeks p.p.	Spontaneous premature labor in eighth month	L	D	
b	658	Mühlbaum, 1913	22	M	II	Yes	....	No	3	2 weeks p.p.	Induced abortion in third month	L	D	Psychosis
c	659	Mühlbaum, 1913	..	M	III	Yes	....	....	*	P.p.	Induced abortion	L	D	*Onset of chorea early in pregnancy
d	660	Mühlbaum, 1913	26	M	IV	Yes	....	Yes	1	Until death	Vaginal extirpation of uterus	D	D	Autopsy: recent endocarditis, parenchymatous nephritis
550	661	Sorbi, 1914	23	M	I	Yes	....	?	4	*	Spontaneous labor at term	L	..	*Chorea persisted in mild form
551* to 570	662* to 681	Shaw, 1914	..	..	..	....	....	....	*	.....	.....	..	..	*Twenty cases with recovery in each case; no other data
571* to 598	682* to 709	Wall and Andrews, 1914	..	..	..	....	....	....	*	.....	.....	..	..	*Twenty-eight cases with recovery in each case; no other data
599	710	Kolde, 1914	20	M	II	No	No	?	7	12 days p.p.	Spontaneous labor at term	L	L	Chorea complicated by psychosis; first pregnancy ended with miscarriage
600	711	Ayers, 1915	27	..	..	....	....	No	.	Until death	Induced abortion	D	D	Albuminuria
601	712	Ayers, 1915	18	..	..	....	No	No	.	Until death	Induced abortion	D	D	
602	713	Ayers, 1915	23	..	..	....	....	Yes	1	2 weeks p.p.	Induced abortion in fourth month	L	D	

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report‡	Age	Social Status§	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea¶	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
603a	714	Albrecht, 1915	20	..	I	....	....	....	.	P.p.	Spontaneous labor at term	L	..	
b	715	Albrecht, 1915	22	..	II	Yes	?	No	2	A.p. in fifth month	.....	..	..	Cure of chorea attributed to injections of blood serum of pregnant woman
604	716	Matthews, 1916	24	M	IV	....	Yes	....	1	P.p.	Induced abortion in second month	L	D	First three pregnancies normal, but these antedated the attack of rheumatism
605	717	Haneborg, 1916	..	..	..	Yes	....	....	.	.....	.....	..	..	Patient twice improved under treatment with thymus gland by mouth
606	718	Vetlesen, 1916	24	M	II	....	No	....	4	.....	.....	..	..	Emotional disturbance before onset of the chorea
607	719	Flamma, 1917	21	M	I	No	No	....	*	10 days p.p.	Induced abortion in third month	L	D	*In first third of pregnancy
608	720	Schuster, 1920	22	M	II	Yes	....	Yes	1	Until death	Spontaneous abortion in third month	D	D	Death fifty-seven days after onset of chorea; first attack of chorea shortly after first labor; fever; pulse rate, 120; for autopsy see text
609	721	Royston, 1920	20	M	I	Yes	Yes	Yes	.	.....	Spontaneous labor at term	L	..	This case considered to be possibly one of pseudosclerosis
610	722	Royston, 1920	20	M	I	No	Yes	Yes	2	3 weeks p.p.	Curettage in second month	L	D	Mental stress preceded onset of the chorea and acute mania complicated it
611	723	Royston, 1920	25	M	I	....	No	....	2	5 weeks p.p.	Curettage in second month	L	D	Worry before onset; fever and acute mania with the attack; leukocytosis, 28,500; second pregnancy normal
612	724	Royston, 1920	21	M	II	....	No	....	3	9 days p.p.	Spontaneous abortion in fourth month	L	D	Temperature, 108 F.; leukocytosis of 23,600; acute mania; albumin and casts in urine; first pregnancy normal
613	725	Royston, 1920	21	S	I	Yes	....	Yes	3	Until death	Induced abortion in fifth month	D	D	Albuminuria; blood pressure, 99 systolic and 62 diastolic; mania; temperature, 106.8 F.; blood cultures negative
614	726	Royston, 1920	25	M	IV	No	No	Yes	6	Until death	Accouchement forcé in eighth month	D	D	First three pregnancies normal; albuminuria; leukocytosis, 15,800; temperature, 109.6 F.; mania; blood pressure, 125 systolic and 78 diastolic; death on eighth day post partum; blood cultures negative

death on eighth day post partum; blood cultures negative

615	727	Couvelaire, 1920	29	..	II	No	No	....	-	.....	.....	..	..	
616	728	Carnot and Gardin, 1920	20	..	I	....	....	....	5	Until death	Died undelivered	D	D	Fever, delirium, purpuric eruption; albuminuria; cultures from blood and cerebrospinal fluid negative
617a	729	Audebert, 1920	28	..	I	Yes	....	....	*	*	Spontaneous labor at term	L	L	*Chorea since 6 years of age; present at conception and continued post partum
b	730	Audebert, 1920	37	..	II	Yes	....	....	*	*	Spontaneous labor at term	L	L	*Chorea since 6 years of age; present at conception and continued post partum
618	731	Mathaei, 1920	20	M	I	Yes	....	No	3	P.p.	Induced abortion in fourth month	L	D	Patient given 30 cc. of blood serum of normal pregnant woman; marked improvement four days post partum
619	732	Genova, 1921	33	..	V	....	Yes*	?	3	P.p.	Induced abortion in sixth month	L	D	*Attack of acute rheumatism during pregnancy, just before chorea developed; no albuminuria; Wassermann reaction negative; blood pressure, 130 systolic; leukocytosis, 13,500
620	733	Genova, 1921	25	..	V	....	Yes*	No	6	11 days p.p.	Induced abortion in sixth month	L	D	*Attack of acute rheumatism during pregnancy, just before chorea developed; no albuminuria; blood pressure, 136 systolic
621	734	Allard, 1921	20	..	..	No	No	?	2	A.p.	Spontaneous labor at term	L	L	Fright preceded attack; chorea followed epidemic encephalitis
622	735	Allard, 1921	..	..	..	No	....	....	1	2 months p.p.	Spontaneous abortion in second month	L	D	
623	736	Allard, 1921	17	..	I	Yes	....	....	8	.....	.....	L	..	
624	737	Allard, 1921	..	..	..	....	....	....	2	A.p. in eighth month	.....	L	..	
625	738	Allard, 1921	..	..	..	....	....	....	3	P.p.	.....	L	..	
626	739	Allard, 1921	19	..	I	No	....	....	3	P.p.	Spontaneous premature labor in eighth month	L	L	No albuminuria; second pregnancy free from chorea
627	740	Allard, 1921	21	M	III	No	....	?	6	Until death	Spontaneous labor at term	D	L	Fever; autopsy: heart muscle softened, congestion of brain and cord; albuminuria; first two pregnancies free from chorea
628	741	Allard, 1921	30	M	II	No	No	....	3	Until death	Induced abortion in third month	D	D	Fever; no albuminuria; first pregnancy free from chorea
629a	742	Allard, 1921	18	M	I	No	Yes	....	1	A.p. in seventh month	.....	L	..	
b	743	Allard, 1921	..	M	II	Yes	Yes	....	1	A.p. in second month	.....	L	..	
630a	744	Allard, 1921	..	..	I	Yes	Yes	....	2	P.p.	Spontaneous abortion in sixth month	L	D	
b	745	Allard, 1921	..	..	II	Yes	Yes	....	1	.....	Spontaneous premature labor in eighth month	L	..	No albuminuria
c	746	Allard, 1921	27	..	III	Yes	Yes	....	1	A.p. in fifth month	Spontaneous premature labor in seventh month	L	D	Relapse of chorea ten days post partum

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother*	Result for Child¶	Comment
631a	747	Allard, 1921	18	M	I	Yes	....	....	1	2 months p.p.	Spontaneous abortion in sixth month	L	D	Marked albuminuria
b	748	Allard, 1921	20	M	II	Yes	....	....	1	.....	Spontaneous premature labor	L	D	Marked albuminuria; ablatio placentae
c	749	Allard, 1921	21	M	IV	Yes	....	....	4	.....	Spontaneous abortion in fourth month	L	D	No albuminuria; third pregnancy ended in abortion, but there was no chorea
632a	750	Allard, 1921	24	..	I	Yes	....	....	1	P.p.	Spontaneous abortion in fifth month	L	D	*
b	751	Allard, 1921	26	..	II	Yes	....	....	1	A.p. in seventh month	Spontaneous abortat term	L	D	
633a	752	Allard, 1921	..	..	I	Yes	Yes	....	*	P.p.	Induced abortion in third month	L	D	*Onset of chorea before third month
b	753	Allard, 1921	..	..	II	Yes	Yes	....	.	P.p.	Spontaneous abortion in sixth month	L	D	
c	754	Allard, 1921	..	..	V	Yes	Yes	....	.	P.p.	Induced abortion	L	D	No chorea in third or fourth pregnancies, but both babies died
d	755	Allard, 1921	30	..	VI	Yes	Yes	....	.	*	Spontaneous labor at term	L	L	*Chorea continued post partum
634a	756	Allard, 1921	20	..	I	....	Yes	Yes	1	P.p.	Spontaneous labor at term	L	L	
b	757	Allard, 1921	23	..	II	Yes	Yes	Yes	1	.....	Spontaneous labor at term	L	L	Slight albuminuria
635* to 661	758* to 784	Allard, 1921	..	..	..	....	....	....	.	.....	.....	..	..	*Twenty-seven cases with recovery in each case; no other data
662	785	Sicard, 1921	35	..	..	....	....	....	3	3 weeks p.p.	Induced abortion in third month	L	D	Delirium; fifteen months later patient developed parkinsonian syndrome
663	786	Meurer, 1921	..	M	VI	....	....	....	8	P.p.	Spontaneous labor at term	L	L	No albuminuria
664a	787	Meurer, 1921 (DeSnoo)	..	..	I	....	....	....	3	A.p. in eighth month	.....	L	..	
b	788	Meurer, 1921 (DeSnoo)	25	..	II	Yes	....	....	6	P.p.	Spontaneous labor at term	L	..	No albuminuria
665a	789	Meurer, 1921 (DeSnoo)	..	..	I	Yes	....	....	*	A.p.	.....	L	..	*Chorea present before pregnancy began

b	790	Meurer, 1921 (DeSnoo)	..	..	II	Yes	....	....	4	P.p.	.....	L	..	
c	791	Meurer, 1921 (DeSnoo)	25	..	IV	Yes	....	....	5	.....	Spontaneous labor at term	L	..	Slight albuminuria; third pregnancy normal
666a	792	Meurer, 1921 (DeSnoo)	26	..	I	....	....	....	.	.....	.....	L	..	
b	793	Meurer, 1921 (DeSnoo)	32	..	II	Yes	....	....	*	P.p.	.....	L	..	*Onset of chorea in middle trimester of pregnancy; no albuminuria
667a	794	Meurer, 1921 (DeSnoo)	19	S	I	Yes	....	....	*	P.p.	Induced abortion in fourth month	L	D	*Onset of chorea early in pregnancy
b	795	Meurer, 1921 (DeSnoo)	..	..	II	Yes	....	....	*	P.p.	Induced abortion in third month	L	D	*Onset of chorea early in pregnancy
668	796	Fruhinsholz, 1922	24	M	I	Yes	Yes	Yes	6	12 days p.p.	Spontaneous abortion in sixth month	L	D	Fright preceded attack; slight albuminuria
669	797	McLean, 1922	22	M	I	Yes	Yes	?	.	.....	Spontaneous labor at term	L	..	No albuminuria
670a	798	McLean, 1922	..	..	I	No	Yes	....	.	.....	Induced premature labor in seventh month	L	..	Fright preceded attack
b	799	McLean, 1922	..	..	II	Yes	Yes	....	*	.....	Spontaneous abortion in third month	L	D	*Onset of chorea before third month; fright preceded attack
c	800	McLean, 1922	26	M	III	Yes	Yes	....	4	A.p. in ninth month	Spontaneous labor at term	L	L	
671	801	Ronsisvalle, 1922	35	M	II	....	....	No	9	2 weeks p.p.	Spontaneous labor at term	L	L	Slight albuminuria; casts in urine; leukocytosis of 8,200; first pregnancy normal
672	802	Flamma, 1922	29	..	I	....	....	....	4	.....	Spontaneous labor at term	L	L	
673	803	Marie, Bouttier and Trétiakoff, 1923	21	M	I	No	....	....	1	Until death	Died undelivered in second month	D	D	For autopsy see text
674	804	Levi, 1923	21	M	I	Yes	....	No	5	P.p.	Spontaneous labor at term	L	L	No albuminuria; leukocyte count, 5,600
675	805	Levi, 1923	21	M	I	Yes	Yes	Yes	1	.....	.....	..	..	No albuminuria; leukocyte count, 7,800
676	806	Hué, 1923	27	M	I	....	No	....	4	A.p. in seventh month	Spontaneous labor at term	L	L	Choreiform movements intermittent; hysteria
677	807	Anderodias, 1924	15	..	I	No	No	No	7	2 weeks p.p.	Spontaneous premature labor	L	L	
678	808	Creutzfeldt, 1924	23	*	II	No	No	No	4	Until death	Spontaneous premature labor in eighth month	D	L	*Patient married during pregnancy; death three days post partum; for autopsy see text
679	809	Jacoby, 1925	18	S	I	Yes	Yes	....	2	2 weeks p.p.	Induced abortion in third month	L	D	No albuminuria
680	810	Jacoby, 1925	30	M	V	....	....	....	6	2 weeks p.p.	Spontaneous premature labor in seventh month	L	L	Attack followed emotional disturbance and blow on abdomen; no fever; blood normal; blood pressure, 115 systolic
681	811	Jacoby, 1925	..	M	IV	....	....	....	6	.....	Spontaneous premature labor in seventh month	L	L	Positive Wassermann reaction
682	812	Jacoby, 1925	20	M	II	Yes	....	No	8	Until death	Abdominal cesarean section in eighth month	D	..	Fever and tachycardia; first pregnancy normal
683	813	Urechia and Elekes, 1925	25	..	II	Yes	....	Yes	3	Until death	Induced abortion in third month	D	D	First attack of chorea six months after first labor; mania; for autopsy see text

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
684	814	Castagna, 1925	29	M	I	No	No	No	9	A.p. in ninth month	Spontaneous labor at term	L	L	Albuminuria; casts in urine; blood pressure, 106 systolic; red blood cell count, 6,100,000; leukocyte count, 8,000; temperature, 35.6 C. (96 F.)
685	815	Groené, 1925	22	..	I	Yes	....	....	7	Until death	Vaginal hysterotomy	D	..	High fever
686	816	Groené, 1925	22	..	*	No	....	....	.	P.p.	Vaginal hysterotomy	L	..	*Multipara; high fever
687	817	Winkelman, 1926 (Burr and Dawes)	20	..	I	....	....	....	2	Until death	Abdominal cesarean section in sixth month	D	D	Albuminuria; casts in urine; died two days post partum; for autopsy see text
688	818	Sickel, 1926	27	M	I	Yes	....	No	6	A.p.	Spontaneous labor at term	L	L	Patient given 15 cc. of blood serum of normal pregnant woman
689	819	Kaffesieder, 1926	32	M	I	Yes	....	....	*	*	Spontaneous labor at term	L	L	*Chorea was present for three years before beginning of pregnancy and persisted post partum
690	820	Kaffesieder, 1926	17	M	I	....	Yes	....	6	10 days p.p.	Spontaneous labor at term	L	L	
691	821	Kaffesieder, 1926	..	M	III	....	....	....	.	10 days p.p.	Spontaneous labor at term	L	L	First two pregnancies free from chorea
692	822	Whitmore, 1926	30	M	IV	No	No	....	3	Until death	Spontaneous abortion in third month	D	D	No fever or leukocytosis; death on twelfth day post partum from exhaustion
693	823	Laurentie, 1926	..	M	III	....	....	....	8	A.p.	Spontaneous labor at term	L	L	No fever or albuminuria; attack lasted about one week
694	824	von Lehoczky-Semmelweis, 1926	23	M	II	....	Yes	....	4	Until death	Induced premature labor	D	..	Death on second day post partum; patient was given blood serum from normal pregnant woman; for autopsy see text
695a	825	Campbell, 1928	..	M	I	No	No	....	*	*	Spontaneous labor at term	L	..	*Chorea limited to slight twitching of right arm on day of delivery
b	826	Campbell, 1928	26	M	II	Yes	No	No	7	About 1 month p.p.	Abdominal cesarean section in eighth month	L	L	Urinalysis, Wassermann reaction, blood cultures and nonprotein nitrogen all negative; blood pressure, 110 systolic and 72 diastolic; hallucinations and persecutory delusions
696	827	Campbell, 1928	27	M	II	Yes	....	....	3	.....	Induced labor in ninth month	L	L	Pregnancy also complicated by toxemia; albuminuria; blood pressure reached 180 systolic and 130 diastolic

697	828	Selitzky, 1928	21	..	I	Yes	....	....	2	5 weeks p.p.	Induced abortion in second month	L	D	
698	829	Selitzky, 1928	19	..	I	Yes	Yes	....	7	.....	Induced premature labor in eighth month	L	L	
699	830	Selitzky, 1928	19	..	I	No	Yes	....	2	1 year p.p.	Spontaneous labor at term	L	L	Patient received an injection of 20 cc. of normal horse serum
700	831	Selitzky, 1928	19	..	I	Yes	Yes	....	6	.....	.....	..	..	Albuminuria
701	832	Selitzky, 1928	..	..	I	....	....	....	2	.....	.....	..	..	Improvement followed injection of normal horse serum
702	833	Selitzky, 1928	20	..	I	Yes	No	....	8	A.p.	Spontaneous labor at term	L	L	History of many attacks of tonsillitis; chorea improved following injection of normal horse serum
703	834	Selitzky, 1928	21	..	I	....	....	....	5	.....	.....	..	..	Albuminuria
704a	835	Selitzky, 1928	..	..	I	No	....	....	.	.....	Spontaneous labor at term	L	L	
b	836	Selitzky, 1928	..	..	II	Yes	....	....	.	.....	.....	L	L	
c	837	Selitzky, 1928	23	..	III	Yes	....	....	3	Until death	Induced premature labor in seventh month	D	D	Autopsy: fatty degeneration of various organs
705	838	Hunter, 1928	21	M	I	No	No	Yes	7	1 day p.p.	Spontaneous labor at term	L	L	
706a	839	Stone and Markson, 1928	18	M	I	Yes	No	....	8	.....	Induced premature labor	L	..	
b	840	Stone and Markson, 1928	21	M	II	Yes	No	No	7	P.p.	Induced labor at at term	L	L	Sedative treatment, quiet and rest; attack persisted mildly to term
707	841	de Michell, 1929	31	M	II	....	....	No	8	P.p.	Spontaneous labor at term	L	L	Albuminuria; Wassermann reaction negative
708	842	Hunnicut, 1929	23	..	I	Yes	....	?	7	3 weeks p.p.	Cesarean section in eighth month	L	L	Acute articular rheumatism complicating the puerperium; diseased tonsils
709	843	Periera de Camargo, 1929	17	..	I	....	....	....	1	P.p.	Vaginal cesarean section in seventh month	L	D	
710	844	Berg, 1930	19	M	I	No	No	?	6	P.p.	Spontaneous labor at term	L	L	Severe postpartum infection; chorea still persisted slightly six weeks post partum
711a	845	Berg, 1930	..	..	I	Yes	....	....	.	P.p.	.....	L	..	
b	846	Berg, 1930	21	..	II	Yes	....	....	.	P.p.	Spontaneous labor at term	L	L	
†712	847	Applegate, J. C., Philadelphia	25	..	I	No	No	No	7	P.p.	Induced premature labor	L	L	Chorea attributed to toxemia of pregnancy
†713	848	Applegate, J. C., Philadelphia	30	..	I	Yes	No	No	4	P.p.	Induced abortion	L	D	Chorea attributed to toxemia of pregnancy
†714a	849	Applegate, J. C., Philadelphia	22	..	I	No	No	No	3	P.p.	Induced abortion	L	D	Chorea attributed to toxemia of pregnancy
b	850	Applegate, J. C., Philadelphia	24	..	II	Yes	No	No	6	P.p.	Induced premature labor in seventh month	L	L	Chorea attributed to toxemia of pregnancy
c	851	Applegate, J. C., Philadelphia	27	..	III	Yes	No	No	7	A.p. in seventh month*	Spontaneous labor at term	L	L	*Attack lasted two weeks; chorea attributed to toxemia of pregnancy
†715	852	Bell, J. N., Detroit	25	..	I	....	....	....	5	Until death	.....	D	..	
†716	853	Bishop, E., Brooklyn	24	M	II	No	No	No	2	About 10 days p.p.	Induced abortion in second month	L	D	

TABLE I.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea‖	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
†717	854	Bovee, J. W., Washington, D.C.	22	..	II	....	....	....	7	P.p.	Spontaneous premature labor	L	L	
†718	855	Carrington, W. J., Atlantic City, N.J.	24	M	I	No	No	No	3	A.p.*	Spontaneous labor at term	L	L	*Chorea ceased after tonsillectomy
†719	856	Dorsett, L., St. Louis	16	S	I	No	No	Yes	6	Until death	Died undelivered in sixth month	D	D	Severe attack of chorea controlled by intramuscular injections of magnesium sulphate; death, due to pneumonia, on twelfth day of disease
†720a to m	857* to 869	Fraser, J., Montreal, Canada	..	..	..	....	....	....	.	.....	.....	..	..	*Patient had chorea from 7 to 14 years of age; aborted seven times; the full term children either were very delicate or died in infancy; no evidence of heart disease
†721a	870	Findley, P., Omaha	30	M	I	....	No	No	1	P.p.	Spontaneous labor at term	L	L	
b	871	Findley, P., Omaha	32	M	II	Yes	No	No	1	P.p.	Abdominal hysterotomy in second month	L	D	
†722	872	Geist, S., New York	22	..	I	Yes	No	No	5	A.p. in sixth month	Spontaneous labor at term	L	L	Patient had the stigmas of endocrine disturbance
†723	873	Goodman, S. J., Columbus, Ohio	24	M	I	No	No	No	3	10 weeks p.p.	Vaginal hysterotomy in third month	L	D	Unilateral chorea
†724	874	Heaney, N. S., Chicago	24	..	I	No	No	No	4	P.p.	Vaginal hysterotomy	L	D	
†725	875	Heaney, N. S., Chicago	25	..	IV	No	Yes	No	3	P.p.	Vaginal hysterotomy	L	D	Patient sterilized
†726	876	Kantz, F. A. S., Cincinnati	23	..	I	Yes	Yes	Yes	5	A.p. in seventh month	.....	L	..	
†727	877	Kotz, J., Washington, D.C.	27	M	III	No	No	Yes	*	5 days p.p.	Spontaneous labor at term	L	L	*Onset of chorea during labor; temperature, 104 F.; pulse rate, 160; irrational; severe tonsillitis and cervical adenitis in fifth month of pregnancy

†728	878	Lawson, H. W., Washington, D.C.	19	M	I	No	No	....	3	A.p.	Spontaneous premature labor in ninth month	L	L	Blood pressure, 120 systolic and 90 diastolic; Wassermann reaction negative; blood normal
†729	879	Litzenberg, J. C., Minneapolis	25	M	I	No	No	No	4	P.p.	Induced abortion in sixth month	L	D	Immediate improvement after the abortion
†730	880	Litzenberg, J. C., Minneapolis	..	..	..	Yes	....	....	.	A.p.	.....	L	..	
†731	881	Longaker, D., Philadelphia	19	M	I	Yes	?	Yes	5	P.p.	Spontaneous labor at term	L	D	
†732	882	Los Angeles General Hospital	15	..	I	Yes	Yes	No	2	.....	Spontaneous abortion	L	D	
†733	883	Los Angeles General Hospital	18	..	I	Yes	Yes	Yes	1	P.p.	Spontaneous labor at term	L	L	
†734	884	Los Angeles General Hospital	37	..	V	Yes	....	Yes	*	P.p.	Induced abortion	L	D	*Chorea ever since fourth labor; patient sterilized
†735	885	Los Angeles General Hospital	16	..	I	Yes	No	No	3	A.p. in fourth month	.....	L	..	
†736	886	Los Angeles General Hospital	19	..	I	No	No	No	5	P.p.	Spontaneous labor at term	L	L	
†737	887	Lull, C. B., Philadelphia	18	S	I	Yes	No	No	7	Until death	Abdominal cesarean section in ninth month	D	D	Temperature, 104 F.
†738	888	Lull, C. B., Philadelphia	21	M	I	Yes	No	No	4	A.p. in fifth month	Spontaneous labor at term	L	L	
†739a	889	Mann, B., Philadelphia	25	M	I	No	No	Yes	2	P.p.*	Induced abortion	L	D	*Attack lasted one month in all
† b	890	Mann, B., Philadelphia	28	M	II	Yes	No	Yes	3	P.p.*	Induced abortion	L	D	*Attack lasted five weeks in all
†740	891	Muller, W. K., Philadelphia	18	..	I	Yes	?	No	*	*	Spontaneous labor at term	L	L	*Chorea present many years before pregnancy and continued post partum
†741	892	Mendenhall, A. M., Indianapolis	26	M	I	Yes	No	Yes	3	P.p.*	Spontaneous abortion in third month	L	D	*Attack lasted two weeks
†742	893	Newell, F. S., Boston	16	..	I	Yes	....	....	5	A.p.*	Spontaneous labor at term	L	L	*Attack lasted three weeks
†743	894	Newell, F. S., Boston	24	..	I	Yes	....	Yes	4	.....	.....	..	..	
†744	895	Nicholson, W. R., Philadelphia	19	M	I	Yes	Yes	No	3	A.p. in fifth month	Spontaneous labor at term	L	L	
†745	896	Norris, C. C., Philadelphia	30	M	II	Yes	No	No	3	A.p. in sixth month	Spontaneous labor at term	L	L	
†746	897	Norris, C. C., Philadelphia	22	M	I	Yes	No	No	8	1 month p.p.	Spontaneous labor at term	L	L	
†747	898	Pirrung, J. E., Cincinnati	21	..	I	No	No	No	4	A.p. in sixth month	Spontaneous labor at term	L	L	

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
†748	899	Pirrung, J. E., Cincinnati	..	..	..	....	....	....	.	.....	Induced abortion in fourth month	L	D	
†749	900	Pirrung, J. E., Cincinnati	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	..	
†750	901	Porter, W. D., Cincinnati	..	..	..	....	....	....	.	.....	Spontaneous labor at term	L	L	
†751	902	Potter, I. W., Buffalo	30	M	I	No	No	No	4	P.p.	Spontaneous labor at term	L	L	
†752	903	Potter, I. W., Buffalo	32	M	II	Yes	Yes	Yes	8	P.p.	Spontaneous labor at term	L	L	
†753a	904	Potter, I. W., Buffalo	20	M	I	Yes	Yes	No	5	.....	Spontaneous labor at term	L	L	
b	905	Potter, I. W., Buffalo	22	M	II	Yes	Yes	No	7	.....	Spontaneous labor at term	L	L	
†754	906	Richards, J. L., Philadelphia	20	M	I	Yes	No	No	*	*	Spontaneous labor at term	L	L	*Chorea present at beginning of pregnancy and continued post partum
†755	907	Scott, A. J., Jr., Los Angeles	25	..	III	Yes	Yes	No	5	P.p.	Spontaneous labor at term	L	L	Mild psychosis with the chorea
†756	908	Scott, W. A., Toronto, Canada	21	M	..	Yes	....	Yes	3	P.p.	Induced abortion in fourth month	L	D	Patient developed mania and was sent to an asylum
†757	909	Scott, W. A., Toronto, Canada	22	M	III	....	....	No	2	P.p.	Induced abortion	L	D	No chorea in two previous pregnancies
†758	910	Scott, W. A., Toronto, Canada	20	M	I	Yes	No	No	2	P.p.	Induced abortion	L	D	
†759	911	Scott, W. A., Toronto, Canada	23	M	I	No	No	....	5	P.p.	Spontaneous labor at term	L	L	
†760	912	Scott, W. A., Toronto, Canada	21	M	I	Yes	....	No	*	P.p.	Spontaneous labor at term	L	L	*Chorea present at beginning of pregnancy
†761	913	Scott, W. A., Toronto, Canada	17	M	I	Yes	....	Yes	*	*	Spontaneous abortion in sixth month	L	D	*Chorea present at beginning of pregnancy and continued post partum
†762	914	Scott, W. A., Toronto, Canada	16	M	..	Yes	....	No	*	.....	.....	..	..	*Chorea present at beginning of pregnancy

†763	915	Scott, W. A., Toronto, Canada	19	S	I	Yes	....	Yes	*	.....	.....	..	..	*Chorea present at beginning of pregnancy; patient improved after the extraction of fourteen infected teeth
†764	916	Scott, W. A., Toronto, Canada	16	S	..	Yes	....	No	.	P.p.	Spontaneous labor at term	L	L	
†765	917	Scott, W. A., Toronto, Canada	17	S	I	Yes	Yes	Yes	*	P.p.	Vaginal hysterotomy	L	D	*Chorea present at beginning of pregnancy
†766	918	Scott, W. A., Toronto, Canada	25	M	..	Yes	No	Yes	2	.....	Spontaneous abortion	L	D	Fright preceded the attack of chorea
†767	919	Scott, W. A., Toronto, Canada	21	S	I	Yes	....	No	2	P.p.	Spontaneous labor at term	L	L	
†768	920	Scott, W. A., Toronto, Canada	30	M	IV	....	....	....	7	P.p.	Spontaneous labor at term	L	L	
†769	921	Scott, W. A., Toronto, Canada	15	S	I	....	Yes	No	3	*	Spontaneous premature labor in seventh month	L	D	*Chorea continued post partum
†770	922	Scott, W. A., Toronto, Canada	..	M	I	....	....	No	3	P.p.	Induced abortion	L	D	
†771	923	Scott, W. A., Toronto, Canada	20	S	..	Yes	?	No	.	P.p.	Spontaneous labor at term	L	D	
†772	924	Scott, W. A., Toronto, Canada	23	M	..	....	....	....	.	P.p.	Spontaneous labor at term	L	L	
†773a	925	Scott, W. A., Toronto, Canada	20	M	II	Yes	....	....	.	.....	.....	L	..	First pregnancy free from chorea
b	926	Scott, W. A., Toronto, Canada	21	M	III	Yes	....	?	5	A.p.	.....	L	..	
†774	927	Spalding, A. B., San Francisco	26	..	III	No	Yes	Yes	2	P.p.	Spontaneous labor at term	L	L	Two recurrences of the chorea during this pregnancy
†775	928	Swift, J. B., Jr., Boston	28	M	I	Yes	Yes	No	2	P.p.	Spontaneous labor at term	L	L	
†776	929	Toombs, P. W., Memphis, Tenn.	22	..	I	No	No	No	2	5 weeks p.p.	Induced abortion in second month	L	D	Tonsillectomy at time of abortion; no chorea in second pregnancy
†777	930	van Sweringen, B., Fort Wayne, Ind.	20	S	I	Yes	No	No	3	P.p.	Spontaneous labor at term	L	L	Several recurrences of the chorea during pregnancy and after labor
†778	931	Vaux, N. W., Philadelphia	24	..	I	Yes	No	No	*	*	Abdominal cesarean section at term*	L	L	*Chorea present since 14 years of age and continued for some time post partum; cesarean section for contracted pelvis; no chorea in second pregnancy
†779	932	Vogt, E., Philadelphia	22	M	I	Yes	No	No	3	1 week p.p.	Spontaneous abortion	L	D	
†780a	933	Vogt, E., Philadelphia	20	M	I	Yes	No	No	4	*	Induced abortion in sixth month	L	D	*Chorea persisted post partum
b	934	Vogt, E., Philadelphia	21	M	II	Yes	No	No	4	*	Abdominal cesarean section*	L	D	*Chorea persisted post partum; *patient sterilized by tubal resection
†781	935	Ward, G. W., New York	21	M	I	Yes	....	?	2	.....	.....	..	..	
†782	936	Williams, J. W., Baltimore	30	M	III	Yes	No	Yes	*	.....	Spontaneous labor at term	L	L	*Chorea present when pregnancy began; history of frequent tonsillitis
†783	937	Williams, J. W., Baltimore	17	S	I	Yes	No	No	.	.....	Spontaneous labor at term	L	L	No albuminuria
†784	938	Williams, J. W., Baltimore	18	M	V	No	No	No	7	P.p.	Spontaneous premature labor	L	L	Patient developed a psychosis and died 2 years later in an asylum; no albuminuria

TABLE 1.—*A Tabular Synopsis of the Available Clinical and Pathologic Data of Nine Hundred and Fifty-One Choreic Pregnancies, Occurring in Seven Hundred and Ninety-Seven Persons, Collected from the Entire Literature and from a Questionnaire Sent to Five Hundred and Thirty American Obstetricians—Continued*

For explanation of reference marks see last page of table

Individual Number†	Pregnancy Number	Author and Date of Report	Age	Social Status‡	Parity	History of Previous Chorea	History of Previous Rheumatism	Evidence of Cardiac Disease	Month of Onset of Chorea§	Time of Recovery from Chorea#	Fate of the Pregnancy	Result for Mother¶	Result for Child¶	Comment
†785	939	Williams, J. W., Baltimore	23	M	IV	Yes	Yes	Yes	5	.....	.....	..	..	Albuminuria; no chorea in previous pregnancies
†786	940	Williams, J. W., Baltimore	16	S	I	No	No	No	*	P.p.	Spontaneous labor at term	L	L	*Onset of the chorea early in pregnancy; no albuminuria
†787	941	Williams, J. W., Baltimore	18	S	I	No	No	?	3	A.p. in sixth month	Abdominal cesarean section in eighth month*	L	D	*Operation for eclampsia; patient died a few years later in an asylum
†788	942	Williams, J. W., Baltimore	24	M	I	Yes	No	No	2	P.p.	Spontaneous labor at term	L	L	No albuminuria
†789	943	Williams, J. W., Baltimore	19	M	I	No	No	Yes	6	.....	Spontaneous labor at term	L	L	No albuminuria
†790	944	Williams, J. W., Baltimore	26	M	I	Yes	No	No	7	P.p.	Induced premature labor	L	L	Albuminuria; history of frequent tonsillitis; patient discharged with mental disturbance and died two years later in an asylum
†791	945	Williams, J. W., Baltimore	19	M	I	Yes	No	No	.	.....	Spontaneous labor at term	L	L	Blood pressure normal; no albuminuria; patient had chronically infected tonsils
†792	946	Williams, J. W., Baltimore	19	M	I	No	No	No	3	.....	.....	L	L	No albuminuria; chemical analysis of blood negative; blood pressure normal; chronically infected tonsils
†793	947	Woodward, H. L., Cincinnati	20	M	I	No	No	Yes	2	Until death*	Spontaneous abortion	D	D	*Very severe case; total duration three weeks
†794	948	Woodward, H. L., Cincinnati	23	M	I	No	No	No	3	1 month p.p.	Induced abortion in third month	L	D	Patient's mother had chorea gravidarum
†795	949	Woodward, H. L., Cincinnati	21	M	III	No	No	No	5	.....	.....	..	..	
†796	950	Woodward, H. L., Cincinnati	22	M	I	Yes	No	No	*	.....	.....	..	..	*Chorea present at beginning of pregnancy
†797*	951	Willson and Preece	20	M	I	Yes	No	?	5	1 month p.p.	Induced abortion in sixth month	L	D	*Personal case; for full report see text

† The numbers in this column marked † are cases taken from the questionnaire, and were previously unpublished. a, b, c, etc., indicate successive choreic pregnancies in the same patient.

‡ In this column S indicates single; M, married.

§ In this column, and in others where they appear, the asterisks refer to the data marked with an asterisk in the column headed "Comment."

In this column, A.p. indicates ante partum; P.p., post partum.

¶ In this column, L indicates life; D, death.

pitalization was from 90 to 112 until one week post partum, and then from 74 to 84 until discharge, except at the time of the fever noted, when the pulse reached 150. The urine was normal throughout. On September 4, the blood picture was: hemoglobin, 70 per cent; red cells, 3,460,000; leukocytes, 9,600; polyorphonuclears, 80 per cent; lymphocytes, 18 per cent; eosinophils, 2 per cent.

HISTORY AND REVIEW OF THE LITERATURE

Felix Meyer gave a quotation in Latin from the works of Horstius, published in 1661, as a reference to what is possibly the first case of chorea gravidarum in the literature. The English translation would be as follows: "The following case, which occurred to the wife of a schoolmaster in childbirth, is, I think, of a peculiar nature. For more than twelve years since that event, for some reason or other, the whole of her left side is thus affected. When awake it is constantly in motion, which she cannot control by will. She is perpetually winking her eyes; her lips are continually opening and shutting; her arms keep jumping up; her fingers gesticulate, and her foot is never quiet. Yet all this occurs without feeling pain. But when she is asleep, everything is at rest." Levick stated that in Hecker's "Epidemics of the Middle Ages" there is a quotation from Burton's "Anatomy of Melancholy" that reads: "Tis strange to hear how long they will dance, and in what manner, over stools, forms, tables even, great bellied women sometimes (and never hurt their children) will dance so long that they can stir neither hand nor foot." These references have been accepted by some as the earliest reported cases of chorea gravidarum, but the latter is obviously a reference to the outbreaks of religious mania associated with the cult of St. Vitus, the only relation of which to any type of chorea is that of having provided the common name of St. Vitus' dance, while the former is certainly open to considerable doubt as to the exact nature of the disease described.

In 1850, Sée reported 2 cases of his own and collected 12 from the literature. The earliest of these was attributed to Reidlin, but we have been unable to verify the reference. In 1862, Mosler tabulated 20 cases from the literature, the earliest of which was attributed to Ungen, but this reference could not be verified either. The case of Hand, however, reported in 1807, has been verified. These papers in French and German were followed by an important one read by Robert Barnes, in 1869, before the Obstetrical Society of London and published in its transactions. He reported 2 cases of his own and collected 46 others from various private sources and the literature. The interest aroused by these communications is indicated by the rapidly increasing number of case reports in the literature. The next milestone marking the progress of knowledge was the very able statistical paper by Buist, in 1894, before the Edinburgh Obstetrical Society. This author, after a most

§ In this column, and in others where they appear, the abbreviations refer to the above-mentioned cases.
# In this column, A.p. indicates ante partum; P.p., post partum.
* In this column, I, indicates life; D, death.

exhaustive and meticulous survey of the literature, was able to tabulate a total of 256 cases occurring in 215 persons. These two papers and those of Wall and Andrews, French and Hicks, Shaw and Croft are undoubtedly the outstanding contributions to this subject in English. The German literature has been reviewed by Bamberg (1873), Gowers (1892) and Kroner (1896). By far the most important contribution in German, however, is the article by Pineles in 1913. This author collected 518 choreic pregnancies in 426 persons. The American literature contains little of importance except isolated case reports, with the exception of the recent papers by Royston and Campbell, and one by Newell, in 1901. In France and Germany interest is manifested by the large number of theses and inaugural dissertations on the subject, many containing elaborate compilations of case reports with, unfortunately, much duplication and copying. Vinay, in his "Traité des maladies de la grossesse et des suites de couches," published in 1894, devoted 10 pages to an able presentation of the subject.

Even a cursory examination of this literature will serve to demonstrate a quite remarkable lack of unanimity of opinion among those who have written on the subject, from the earliest articles until those of recent years, as to the nature of chorea gravidarum. In general, however, these divergent views are subject to classification into two groups, as follows: First, the belief that chorea in pregnancy represents a merely accidental association of the two and that the chorea is identical with the ordinary chorea of childhood. Second, the belief that it is entirely different from ordinary chorea; in other words, merely a choreiform condition either directly or indirectly dependent on pregnancy for its production. Some of the opinions that have been expressed on this subject may now be briefly reviewed.

A belief in the essential unity of Sydenham's chorea and chorea gravidarum was expressed as early as 1850 by Sée in the following opinion:[1] "Thus it may be supposed that pregnancy does not constitute the real cause and that it serves only as an intermediary of the actual causes of which it favors the production." In 1901, Launay, in a thesis that contains the best historical account in the literature, said: "It is very certain that Sydenham's chorea, coming on during pregnancy or labor, should not be confused with the tics or with hysterical chorea, for its clinical existence cannot be doubted." In 1903, Wall and Andrews said: "In the first instance it has to be decided whether these cases are truly choreic; it seems necessary in most cases to answer in the affirmative. . . . In fact, no distinguishing feature can be determined which points to any difference from the movements of Sydenham's chorea." In 1906, Poynton and Holmes made their well known "Contribution to the Pathology of Chorea," in which they expressed their belief in its rheumatic nature. They said: "Chorea in pregnancy is probably a rheumatic chorea." They supported this statement with statistics showing the frequency with

1. Direct quotations from the French and German literature are all translations.

which a history of rheumatism is obtained in these cases. In 1913, Pinard quoted Dieulafoy as follows: "Pregnancy generally makes the prognosis of chorea more grave, not that the chorea of pregnant women is a special form, but that, as Jaccoud has clearly shown, the gravid state associated with ordinary chorea aggravates its manifestations." In 1925, Urechia and Elekes stated that F. H. Lewy did not consider chorea in pregnancy as different from ordinary chorea, and they described the two together, giving the same pathology for each.

These views regarding chorea in pregnancy as identical with chorea in childhood find opposition as follows: In 1888, Hocquet expressed the opinion that "hysteria and chorea (in pregnancy) would appear to be two forms of the same malady." In 1891, Riche stated the position of this school of thought in the following words: "The special study which has been made of chorea of pregnancy is well justified. It is not an accidental complication of pregnancy; it is a disease, caused by pregnancy. This is proved by the facts that chorea of pregnancy appears at an age when simple chorea is exceedingly rare; that it lasts much longer than ordinary chorea; and that, finally, it ordinarily does not cease until the uterus has been emptied of its contents. . . . One rarely finds in the etiology of chorea in pregnancy the causes invoked by the majority of authors. One is then forced to admit that pregnancy itself can suffice to provoke the appearance of the chorea, and one can then explain this disease by saying that it is a reflex neurosis of which the point of departure may be the utero-ovarian plexus." In 1893, Duchateau described chorea in pregnancy as "chorée autotoxique," and attributed its causation to an "éclampsie attenuée." In 1899, Giles de la Tourette identified it with the tics. In 1901, Newell stated: "Chorea deserves a special place in the pathology of pregnancy. It is not an accidental complication due to the recurrence of a previous infantile chorea, but in the majority of cases appears for the first time during pregnancy; that is, it is to a great extent produced by pregnancy. Pregnancy is not the only causative factor, but is the fundamental condition on which the other elements in the causation of chorea depend."

In 1908, Shaw, after an admirable study of the subject, reached the following conclusions:

1. "The chorea of pregnancy is due to a toxin which appears to be identical with, or closely to resemble, that of acute rheumatism.

2. "It affects human subjects under two circumstances, both of these being characterized by instability or irritability of the nervous system, namely, childhood and pregnancy.

3. "The cause of the instability or irritability of the nervous system in pregnancy, bringing it down to the level of childhood, is the toxemia of pregnancy."

These views are in substantial accord with those expressed in 1913 by Pinard, who said: "From the point of view of the prognosis of the so-called chorea of pregnancy I do not share medical opinion, nor . . . do I share recent medical views concerning the pathology. Assuredly I believe, with many others, that that which is called chorea should be placed in the category of the neuroses. But I cannot admit that the choreic syndrome is the manifestation of an encephalitis or a meningo-encephalitis. Neither can the recently advanced view that chorea is of syphilitic origin be accepted by any informed physician. Being given the facts which I have observed of the reproductive function with chorea, I believe more than ever in an auto-intoxication manifesting itself by choreic symptoms in predisposed individuals. With Joffroy, I think it is an auto-intoxication, and an evolutionary disease (showing itself at the moment of the grasp of the individual by the species) and, with Latique, I admit that pregnancy prolongs puberty." Finally, there are

the views recently expressed by the eminent neurologist, Sicard, that choreic manifestations in pregnancy are due to epidemic encephalitis. He said: "Chorea of pregnancy sometimes allies itself to epidemic encephalitis. I have had occasion to report cases of the choreic syndrome developing during pregnancy, with choreic gesticulation and delirium without any of the classic signs of encephalitis, that is to say, without diplopia, without rhythmic clonicity, without lethargy, which were followed by a characteristic parkinsonian syndrome, thus indicating their epidemic encephalitic origin, since, in the absence of all diagnostic certainty we have the clinical testimony of the parkinsonism to determine a retrospective diagnosis." And later: "Bringing together this case of chorea of pregnancy followed by parkinsonism and two others of which I have knowledge, which progressed in the same manner toward tremor and hypertonicity, and joining the findings of Carnal and of Harvier with the anatomicopathologic observations reported . . . one cannot but differentiate between chorea of pregnancy and Sydenham's chorea, and connect the former, thanks to the bond of the pathognomonic parkinsonism, to epidemic encephalitis."

From the radically divergent views quoted it will be seen, as has been previously stated, that there are two main schools of thought; one regarding chorea gravidarum as merely Sydenham's chorea occurring during pregnancy, or, more rarely, vice versa, and the other regarding it as an entirely different pathologic entity, merely choreiform in type, either directly dependent on pregnancy for its causation or else a purely accidental complication of it. Our present study has caused us to aline ourselves definitely with the former school and to advance the opinion that there is not one scintilla of clinical or pathologic evidence to justify any conclusion with respect to the essential nature of chorea in pregnancy except that it is Sydenham's chorea modified slightly by the associated pregnancy. Additional evidence of the indirect nature of the association is furnished by the occurrence of chorea in the puerperal period. Buist collected about 20 such cases which, however, have not been included in this series. In 3 cases in table 1 there was prompt recovery from the chorea following delivery, but a relapse occurred in a few weeks and continued for some time. It is, of course, realized that much remains unknown concerning the true nature of the ordinary adolescent type of chorea, but it is at least a well recognized clinical entity. We believe that chorea gravidarum is the same disease entity and will give our reasons for this opinion as we present the analyses of the data of our collected cases. If this be accepted as true, it follows that the term chorea gravidarum, while it has the sanction of long accepted usage, is in reality a misnomer only to be justified by sanctioning such additional terms as pneumonia, typhoid and influenza gravidarum.

FREQUENCY

Chorea is one of the rarest complications of pregnancy. Our search of the literature, with all the facilities of the Surgeon General's Library at our disposal, has resulted in a bibliography of about 330 references,

which, while it does not contain all on the subject, contains the great majority, all of any material importance and all those presenting case reports. In the effort to establish data for an estimation of its frequency in the United States, a questionnaire was sent to 530 members of obstetrical societies throughout the country. Of 170 obstetricians making returns, 53 reported that they had seen chorea gravidarum, and 117 that they had not. Of the 53 reporting cases, 14 reports were too indefinite to be used for purposes of tabulation; the remaining 39 correspondents reported a total of 104 choreic pregnancies in 85 patients. In table 2 there have been assembled all the data found in the literature or from the questionnaire bearing on the question of the frequency of occurrence of this complication in hospital or private obstetrical practice. The result is a total of 119 cases of chorea gravidarum in 270,825 pregnancies, an incidence of 1 choreic pregnancy in 2,275. In 263,625 hospital cases, there were 117 choreic pregnancies, an incidence of 1 in 2,252, as against 2 cases in 7,200 obstetrical patients seen in private practice, an incidence of 1 to 3,600.

These figures have to do with the frequency with which pregnancy is complicated by chorea. For information on the reverse of this question, namely, what proportion of cases of chorea is complicated by pregnancy, we have the data given by the "Reports of the Collective Investigation Committee of the British Medical Association" (Mackenzie), which give 9 cases of chorea gravidarum in 439 cases of chorea reported, or 1.5 per cent.

The question of the relative frequency with respect to geographical distribution is of interest and, it is believed, of importance in connection with the etiology. The reports from 13 hospitals in the United States, representing Boston, New York, Newark, N. J., Philadelphia, Baltimore, Washington, D. C., Fort Wayne, Ind., St. Louis and San Francisco, give 33 cases in 115,554 obstetrical admissions, a proportion of 1 in 3,501. Scott, from the Toronto General Hospital, reported 15 cases in approximately 2,200 admissions, an incidence of 1 in 146. In Europe, the combined reports from the Dublin Rotunda, the Frauenklinik in Leipzig and the Baudelocque Clinic in Paris give 67 cases in 105,871 admissions, an incidence of 1 in 1,580. Myer, from the Woman's Hospital, Melbourne, Australia, reported 2 cases in 40,000 deliveries, an incidence of 1 in 20,000. A comparison of the statistics for Europe and the United States in approximately an equal number of cases shows an incidence of 1 in 1,580 for the former as against 1 in 3,501 for the latter, a relative proportion of 2.2 to 1. As throwing additional light on the frequency in Europe, it may be pointed out that the Dublin Rotunda (Sheill) is reported to have had no case in 20,000 deliveries and the Glasgow Maternity Hospital (Black) only 2 cases in a period of twenty-two years; Wall and Andrews reported 68 cases seen at the

TABLE 2.—*Statistics on the Frequency of Chorea Gravidarum in a Series of Obstetrical Cases from Hospital and Private Practice* *

Reporter	City	Institution	Comment	Total Number Cases	Cases of Chorea Gravidarum	Proportion
Hospital Cases						
United States						
Newell	Boston	Lying-In	Prior to 1901	11,000	13	1 in 846
Newell*	Boston	Lying-In	Since establishment of clinical index	12,559	2	1 in 6,279
Phaneuf*	Boston	Carney	In period of eight years	.....	0	.....
Ward*	New York	Woman's	.....	7,494	1	1 in 7,494
Williams*	Philadelphia	Maternity	.....	1,196	0	.....
Tallant*	Philadelphia	Woman's Medical College	Number of cases approximate	10,000	0	.....
Muller*	Philadelphia	Germantown	Number of cases approximate	3,000	1	1 in 3,000
Boyd*	Philadelphia	Medico-Chirurgical	.....	3,600	0	.....
Ill*	Newark, N.J.	St. Barnabas	Average of 300 deliveries a year	.....	0	.....
Williams*	Baltimore	Johns Hopkins	.....	16,570	11	1 in 1,506
Willson*	Washington, D.C.	Columbia	Number of cases approximate	30,000	2	1 in 15,000
Porter*	Fort Wayne, Ind.	St. Joseph's	.....	2,975	0	.....
Spalding*	San Francisco	Stanford Univ.	.....	5,160	1	1 in 5,160
Berg	St. Louis	City Hospital	Number of cases approximate	12,000	2	1 in 6,000
Total for United States				115,554	33	1 in 3,501
Canada						
Scott*	Toronto	Toronto General	Number of cases approximate	2,200	15	1 in 146
Europe						
Sheil	Dublin	Rotunda	.....	20,000	0	.....
Gentin	Paris	Baudelocque Clinic	1889 to 1899	15,638	15	1 in 1,042
Allard	Paris	Baudelocque Clinic	1899 to 1919	38,882	38	1 in 1,010
Meumann	Leipzig	Frauenklinik	1886 to 1911	31,351	14	1 in 2,200
Total for Europe				105,871	67	1 in 1,580
Australia						
Meyer	Melbourne	Woman's	.....	40,000	2	1 in 20,000
Total for hospital cases				263,625	117	1 in 2,252
Private Practice						
United States						
Mitchel*	Cincinnati	.....	.....	1,000	0	.....
Porter*	Fort Wayne, Ind.	.....	Several thousand cases	.....	0	.....
Moyer*	Philadelphia	.....	Number of cases approximate	2,000	0	.....
Kandels*	Philadelphia	.....	Number of cases approximate	3,000	0	.....
Total for United States				6,000	0	.....
Canada						
Scott*	Toronto	.....	Number of cases approximate	1,200	2	1 in 600
Total for private practice				7,200	2	1 in 3,600
Total for hospital cases				263,625	117	1 in 2,252
Grand total				270,825	119	1 in 2,275

* The series marked with an asterisk are from the questionnaire.

London Hospital between 1882 and 1912; Shaw, 32 cases at St. Mary's Hospital, Manchester; French and Hicks, the cases of 29 patients treated at Guy's Hospital, London, prior to 1906, and Croft, 12 cases in the Women's and Children's Hospital, Leeds, "in the last few years," from the context apparently a period of six years prior to 1910. These reports from Great Britain, France and Germany are in sharp contrast to the situation in southern Europe; several Italian authors, impressed with the amount of attention given the subject in the English, German and French literature, commented on the great rarity of such cases in Italy. Only 1 case is reported for Spain, but Jakoby reported 4 cases observed in Palestine. The significance of this geographical distribution will be commented on later in connection with the association of the disease with rheumatism.

It is thoroughly realized that these statistics are of value only in a general way. There can be no question that in the United States the condition is seen much less frequently in private practice than once in 3,600 pregnancies; how much less it is impossible to say. The indicated incidence of 1 in 3,501 in hospital practice in the United States also undoubtedly gives an exaggerated idea of its frequency, as is evidenced by the previously stated fact that of 170 American obstetricians, 117 reported never having seen a case. In Great Britain the amount of literature on the subject, the number of cases reported and the statistics that have been given for several hospitals clearly indicate a greater frequency there than in this country. The most definite and reliable statistics in the literature are those from the Baudelocque Clinic, in Paris, showing 53 cases in 54,520 obstetrical admissions between 1889 and 1919, a rate of approximately 1 in a little over 1,000. Therefore, this proportion would seem to be definitely established as the frequency for this clinic, although Allard stated that these figures give an exaggerated idea of the frequency in Paris as a whole, since, as he said, "maternities are the refuge of pathological cases." The statistics of Meumann from the Frauenklinik in Leipzig, 14 cases in 31,351 admissions, or 1 in 2,200, show a frequency of somewhat less than one-half that of Paris. The statistics of Scott from the Toronto General Hospital, 15 cases in approximately 2,200 obstetrical admissions, or 1 case in 146, are so out of proportion to all other reports that we are at a complete loss to explain them.

ETIOLOGY

Age.—The age of the patient was definitely stated in 666 cases, the resulting average age being 22.4 years. In chart 1, the age distribution by years is graphically represented in percentages of the total number of cases, and for comparison the same is done for 2,000 white women

delivered at Columbia Hospital for Women, Washington, D. C. In chart 2, the same comparison is presented in percentages between the age distribution by hemidecades of 670 choreic cases and the 2,000 cases mentioned. It will be observed that the curve of the choreic cases shows

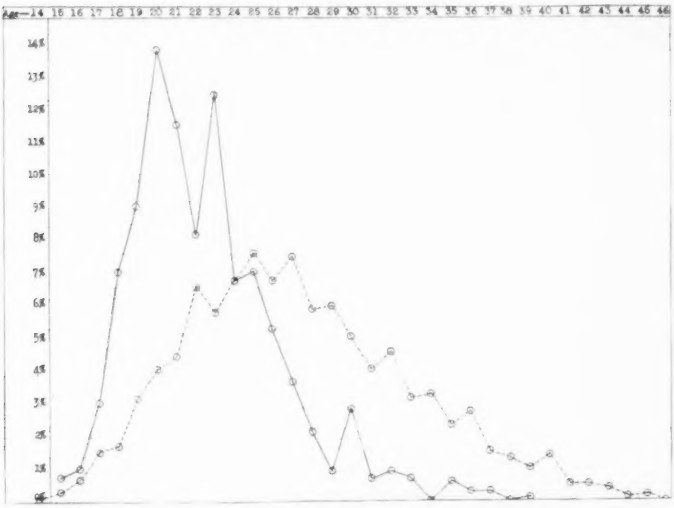

Chart 1.—Comparative age distribution, by years, in percentages of the total number of cases, between 666 collected choreic and 2,000 nonchoreic pregnancies in white women from Columbia Hospital, Washington, D. C. The solid line indicates choreic cases; the dotted line, nonchoreic cases.

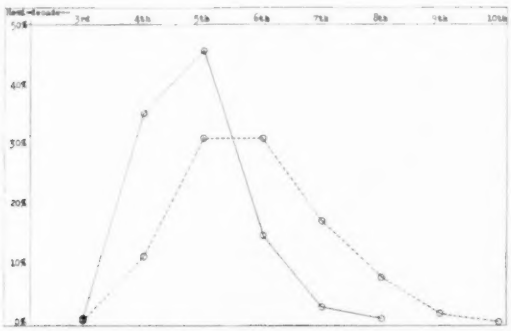

Chart 2.—Comparative age distribution, by hemidecades, in percentages of the total number of cases, between 670 collected choreic and 2,000 nonchoreic pregnancies in white women from Columbia Hospital, Washington, D. C. The solid line indicates choreic cases; the dotted line, nonchoreic cases.

a much larger percentage distributed in the early twenties than does the curve of the control series. The former reaches its peak at the twentieth year; the latter not until the twenty-fifth, while the decline from the peak is much more precipitate in the former than in the latter. In chart 2 it will be observed that the choreic cases exceed the controls in the third, fourth and fifth hemidecades by 0.3, 24 and 14.5 per cent, respectively, while in the sixth, seventh and eighth hemidecades the controls exceed the choreic cases by 17, 14 and 7 per cent. In the ninth hemidecade, 1.75 per cent of the controls was found as against none of the choreic pregnancies. A comparison by decades shows 35.9, 60.2 and 3.7 per cent of the choreic cases distributed in the second, third and fourth decades of life as against 11.4, 61.6 and 25.1 per cent of the controls. If, however, the comparison is made for the first, second and third decades of sexual maturity, the difference is found to be even more striking, as evidenced by the following figures: 74.7, 23.8 and 1.3 per cent of the choreic cases as against 34.7, 53.1 and 11.9 per cent of the controls.

TABLE 3.—*Parity in Seven Hundred and Forty-Six Cases*

	Para													
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	Multiparae
Number of cases.....	414	171	73	38	19	8	2	2	1	1	1	1	2	13

These figures would seem to show conclusively that chorea complicating pregnancy is a disease of young women. In this respect the disease is in accord with Sydenham's chorea, which, as is well known, usually attacks children and young adolescents.

Social Status.—Data on the legitimacy or illegitimacy of the pregnancy were available in 505 cases: Of these, 418 pregnancies were legitimate and 87 illegitimate, an illegitimacy rate of 17.2 per cent. The statement has been made that chorea is more frequent in illegitimate pregnancy, but, while the foregoing rate does seem high, there is obviously no way to check it against any comparable series of cases.

Parity.—The data in 746 cases are available for studying the question of parity distribution. This material has been tabulated in table 3, from which the predominance of the first pregnancy may be seen at a glance. It must be borne in mind, however, as will be seen by reference to table 1, that of the total of 951 choreic pregnancies there were 253 that occurred in 99 persons. This well demonstrated tendency of the disease to attack the same patient in more than one pregnancy has seemed to indicate a further study of the material to determine the parity distribution, by percentages, of the total number of patients suf-

fering from their first attack of chorea gravidarum. Data on this point were available in 509 cases, and have been assembled in graphic form in chart 3, together with a similar study, for comparison, of 2,000 nonchoreic pregnancies from Columbia Hospital for Women, Washington, D. C. It will be seen that in the choreic cases primiparae exceed the controls by 30.5 per cent and are decidedly exceeded by the controls in every other pregnancy.

History of Chorea Previously.—It now becomes necessary to consider the question of the previous history of the patients with respect to chorea. In this connection, the cases were divided into three groups,

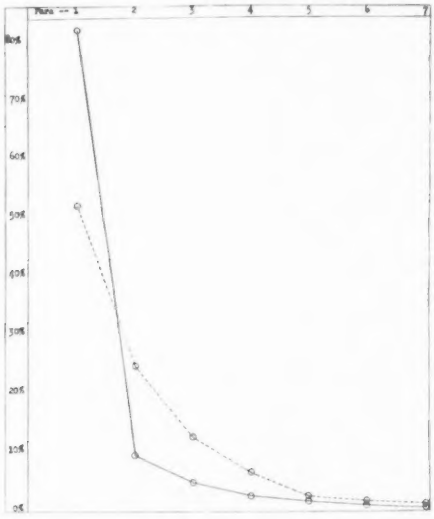

Chart 3.—Comparative parity distribution in percentages of the total number of cases, between 509 first attacks of chorea gravidarum and 2,000 nonchoreic pregnancies in white women, from Columbia Hospital, Washington, D. C. The solid line indicates choreic cases; the dotted line, nonchoreic cases.

namely: Those in which a previous history of chorea was definitely denied; those in which it was admitted and in which, from the context, it could be determined that this was ordinary chorea and not chorea gravidarum, and, finally, those giving a history of a previous chorea which, from the context, could not be definitely so classified. The data of 474 cases were available for this study and are tabulated in table 4. From this table it will be seen that in 474 cases of chorea gravidarum there were 185 patients who definitely denied previous chorea, or 39 per cent; 228 who gave a history of previous chorea

unassociated with pregnancy, or 48.1 per cent, and 61 who gave a history of previous chorea, the relation of which to pregnancy could not be determined, or 12.8 per cent. It would seem to be quite obvious that in the majority of cases in this last group the previous history of chorea referred to ordinary chorea and not to chorea gravidarum, since the occurrence of this complication in more than 1 pregnancy would almost inevitably cause comment by the reporter. On adding these two groups together, the percentage of patients giving a history of previous chorea is increased to 60.9 per cent. But even this figure does not quite give the whole picture. These figures all refer to individuals. If we examine the statistics for pregnancies, rather than individuals, and include the cases in which chorea complicated more than 1 pregnancy as separate choreic pregnancies with a history of previous chorea, we arrive at the following figures: In 628 choreic pregnancies chorea had occurred previously in 443, or 70. 5 per cent, and had not

TABLE 4.—*History of Four Hundred and Seventy-Four Patients Concerning Previous Chorea*

	No. of Cases	Percentage
No chorea previously	185	39.0
History of previous chorea not associated with pregnancy	228	48.1
History of previous chorea, association with pregnancy not determined	61	12.8
Total	474	99.9

occurred in 185, or 29.4 per cent. These figures may be compared with those given by Allard from the Baudelocque Clinic, which showed previous attacks of chorea in 81 per cent of 53 cases.

The opposite question as to the number of women, choreic in childhood or adolescence, in whom chorea develops in a subsequent pregnancy is answered in the literature only by the author just quoted. The statistics of the Baudelocque Clinic show that in 38,382 obstetrical admissions there were 201 patients who gave a history of previous chorea, and of these, 53 had chorea gravidarum. This would indicate that approximately 25 per cent of women who have had chorea in childhood may be expected to have a recurrence during pregnancy.

It seems reasonable to believe that these facts can be explained only on the hypothesis that pregnancy causes a latent disease to become active; any other theory certainly involves overlooking the obvious. Furthermore, it has been shown that chorea occurring for the first time during pregnancy may, and often does, complicate subsequent pregnancies and may finally continue indefinitely post partum.

Association with Rheumatism.—In order to study the association of chorea gravidarum with rheumatism, the cases were divided into

four groups, as follows: First, those in which a history of previous rheumatism was definitely denied; second, those in which it was definitely admitted; third, those in which the rheumatic history was dubious, and, fourth, those in which there was a double complication with chorea and rheumatism in the same pregnancy. There were 404 cases available for this study, which are tabulated in table 5. From this table it will be seen that in 35.3 per cent of 404 cases there was a history of previous rheumatism, while in 4.4 per cent of the cases the choreic pregnancy was also complicated by rheumatism. In this latter group, made up of 18 cases, the rheumatism was synchronous with the chorea in 12 cases, preceded it in 5 cases and followed it in 1 case. By placing these two groups together, we arrive at the figure of 39.7 per cent of the cases either associated with rheumatism or giving a history of it. The real figures may well be in excess of these, however, for, as pointed out by Duckworth, the milder manifestations of rheu-

TABLE 5.—*Association of Chorea Gravidarum with Rheumatism in Four Hundred and Four Cases*

	No. of Cases	Percentage
History of previous rheumatism negative	237	58.6
History of previous rheumatism positive	143	35.3
History of previous rheumatism doubtful	6	1.4
Rheumatism associated with chorea in same pregnancy	18	4.4
Total	404	99.7

matism in childhood usually escape memory. Certain cases in table 1 throw an additional light on this subject. Thus there is the patient of Semple who had never had chorea, but who had acute rheumatic fever a few months before her first pregnancy, in which chorea developed in the first month. The patient of Black had chorea in childhood and a first pregnancy that was normal; later she had acute rheumatic fever, and following this the second and third pregnancies were complicated by chorea. Matthews and Randle each reported the case of a patient with three normal pregnancies, then acute rheumatic fever and chorea in the fourth pregnancy; Genova reported the cases of two patients with four normal pregnancies, then rheumatic fever and chorea in the fifth pregnancy, and Villapadierna reported the case of a patient with the same sequence of events following five normal pregnancies. The patient of Hunnicut had an attack of acute articular rheumatism complicating the puerperium.

The association between rheumatism and Sydenham's chorea is too well known to require comment; the Collective Investigation Committee of the British Medical Association found a definite history of it in 26 per cent and an indefinite history in 14 per cent of their cases.

A comparison of these findings with those just given for chorea gravidarum shows that the incidence of rheumatism in the two series is practically identical. In connection with the association of the disease with rheumatism, its geographical distribution is significant. It has been shown that it is particularly prevalent in Great Britain, to a somewhat less extent in Germany and France, and that it is very rare in southern Europe. Surgeon General Cumming of the Public Health Service is my authority for the statement, significant in this connection, that of all immigrants inspected at Ellis Island, those from Great Britain and Ireland show the highest proportion of rheumatic sequelae.

History of Both Chorea and Rheumatism Previously.—In 339 cases, the histories were definite regarding both chorea and rheumatism.

TABLE 6.—*History of Three Hundred and Thirty-Nine Patients with Respect to Both Chorea and Rheumatism*

	No. of Cases	Percentage
Neither chorea nor rheumatism previously	115	33.9
Both chorea and rheumatism previously	101	29.7
Chorea previously without previous rheumatism	101	29.7
Rheumatism previously without previous chorea	22	6.5
Total	339	99.8

TABLE 7.—*Frequency of Cardiac Disease in Three Hundred and Fifty-Eight Cases*

	No. of Cases	Percentage
Heart normal	183	51.1
Heart definitely diseased	116	32.4
Evidence of disease questionable	59	16.4
Total	358	99.9

These data are given in table 6, from which it will be seen that in over one fourth of the pregnancies there is a history of both chorea and rheumatism, and in approximately two thirds of them, of one or the other or both. It should be further noted that in 24 patients giving a positive history of both diseases previously, there was also definite evidence of cardiac disease.

Evidence of Cardiac Disease.—On this point the available material is made up of 358 pregnancies that have been classified into three groups, namely: Those in which the heart was definitely stated to be normal; those in which there was either definite pathologic evidence of heart disease or a sufficiently detailed clinical report to justify the assumption that disease was present and those in which the clinical evidence presented tended to indicate disease, but was deemed insufficient to make a positive diagnosis. These data are given in table 7.

It will be seen from these figures that heart disease was definitely noted in approximately one third of the cases, or, if we include the group of cases with indefinite evidence of disease, more or less definitely in approximately one-half. These findings coincide closely with those for ordinary adolescent chorea reported by Strong, according to whom, in a series of 2,359 cases reported by 9 authors, there was evidence of organic cardiac disease in 953, or 40.3 per cent. Thus we have demonstrated again a striking similarity between these two types of chorea.

Emotional Disturbance Before the Attack.—In the ordinary chorea of childhood, fright, overstudy, etc., have often been accepted as the immediate predisposing cause of an attack. In 68 cases of chorea gravidarum in this series some form of emotional disturbance, fright, anger, worry, etc., was stated to have preceded the outbreak.

Rarity in the Negro.—Sydenham's chorea is excessively rare in the Negro race, and no case of chorea gravidarum in a Negress is reported in the literature. Too late for incorporation in our statistics, however, a patient with a mild but quite typical case has been admitted to the Georgetown University Hospital.

PATHOLOGY

The data available for study of the pathology are found in the more or less complete reports of 67 autopsies found in the literature from 1824 to 1930, inclusive. As might be expected, much of this material is of little value from the point of view of the modern histopathology of the nervous system, but even the older records contribute some information of value. Interest naturally centers in the heart and central nervous system, but the pathology in other organs must be briefly considered first.

The liver is stated to have been normal in 5 instances, and was the site of parenchymatous degeneration in 3 cases, cloudy swelling twice, congestion once and several small areas of necrosis once. The spleen is reported normal in 5 instances, and was the site of softening once, hyperplasia twice, marked swelling once, passive congestion once, infarcts once and embolism twice. The kidneys are reported normal in 4 cases, and were the site of congestion 5 times, parenchymatous nephritis 4 times, bacterial infarcts once, cloudy swelling twice, fatty degeneration once, embolism 3 times and pyelitis once. The lungs were reported normal 4 times, and the site of congestion 4 times, edema twice, bacterial infarcts once, bronchopneumonia twice, pneumonia and pleurisy once and subpleural hemorrhages once. The uterus and adnexa gave evidence of puerperal infection in 5 instances. Fragmentary as this evidence is, it would seem to point toward an underlying pathology of an infectious nature.

The most striking finding in the autopsy material was the great frequency of cardiac disease. The condition of the heart was mentioned in 46 cases, in 40 of which it was diseased and in only 6 apparently normal, an incidence of cardiac pathology of 86.9 per cent. The most frequent finding was acute, recent endocarditis, often described as ulcerative or vegetative, the mitral valve being the favorite site. Less frequently the disease was described as chronic; or thickening or distortion of the valve flaps was the only pathology present. Myocarditis was present in several instances, but except for ecchymoses beneath it, the pericardium does not seem to have been involved.

In the central nervous system the most frequently mentioned macroscopic finding is congestion of the brain and meninges. This was almost universally noted. Edema was mentioned twice; scattered petechial hemorrhages twice; increased cerebrospinal fluid 3 times; pachymeningitis twice, hemorrhage in 1 case; purulent leptomeningitis once; embolism of the left middle cerebral artery in 2 cases, in 1 of which the embolus lodged beyond the anterior choroid branch and was of the same material as the vegetation on the mitral valve, and there was also an extensive hemorrhage resulting from a rupture of one of the smaller branches of the middle cerebral artery supplying the corpus striatum; thrombosis of several cerebral sinuses once, and in 5 cases the brain was reported as normal. In 10 examinations of the spinal cord, it was reported to be normal 4 times; congestion was noted in the other cases, with an acute inflammation of the meninges once and softening of the cord structure in 4 instances.

The number of studies of the histopathology of the brain are as yet entirely too few to permit any final deductions as to the exact nature of the pathologic changes. They may be summarized as follows:

Elischer (1874), in a patient dying four days post partum, found degeneration in the central ganglions, insula and claustrum; secondary extravasations in the neuroglia with small emboli; congestion of the spinal meninges, and changes in the nerve cells in the cord.

Guinon (1886) reported the brain normal microscopically.

Turner (1892) presented colored plates showing 2 pyramidal cells from the deeper cortical layers of the Rolandic area which were swollen and deformed, with granular cytoplasm, deformed and abnormally stained nuclei, and, in a single instance, loss of the cell outline.

Pelnář (1904), in the case of a woman who died with high fever and fulminating sore throat, found marked congestion of the brain with small hemorrhages, but no evidence of encephalitis. "Chorea bodies" were present, but were considered to be artefacts.

Poynton and Holmes (1906), in a case reported by French and Ricks, found recent thrombi in many vessels around some of which the brain tissue was slightly necrosed and infiltrated with serum. There was some small round cell infiltration into the vessel walls and perivascular lymph spaces. Marked degenerative lesions were noted in the nerve cells. "Micrococci, generally lying as diplococci . . .

were found after careful searching in the pia mater of the fore brain and in the walls of the cerebral vessels."

De Crespigny (1913), in the case reported by Wilson, found numerous scattered capillary hemorrhages from the vessels of the leptomeninges and throughout the substance of the cerebrum. There was intense congestion of the capillaries. The brain was not sufficiently well fixed to enable changes in the nerve cells to be described, if such were present.

Schuster (1920), in a case in which Staphylococcus aureus had been cultured from the blood, found thrombosis associated with hemorrhage in the third frontal and ascending frontal convolutions of the right parietal lobe. The condition of the nuclei of the base was not mentioned. There was also hyperplasia of the neuroglia of the cerebral cortex.

Marie, Boutier and Trétiakoff (1923) presented one of the most complete and extensive histopathologic studies in the literature. They said: "The histologic examination of the nervous centers discloses the existence of two parallel pathologic processes; an exudative meningitis, accompanied by an abundant hemorrhagic exudate in the adventitial coats of the vessels of the base of the brain, and numerous small toxi-infectious nodules disseminated in the cerebral mass." The meningeal exudate contained much fibrin, and the red cells greatly predominated over the leukocytes. The endothelial cells of the vessel walls were irritated and proliferated, but the walls were intact. In the cerebral cortex numerous toxi-infectious nodules of the size of a pinhead were found, made up of proliferated neuroglia cells surrounding one or two capillaries, some containing granules of myelin. At the site of the nodules the nerve cells are distinctly altered and some axis cylinder processes are altered and capped by terminal enlargements, and the adjacent tissues are edematous. "To summarize, there are small nodular lesions, destructive (or degenerative), where the phenomena of reaction are reduced to edema and a proliferation of neuroglia cells . . . ; the influence of leukocytes is entirely absent." In the centrum ovale and the corpus optostriatum, the same two pathologic processes were noted. "The sub-optic region, the cerebral peduncles, the medulla and the cerebellum seemed to be spared by the morbid process."

Creutzfeldt (1924) found intense congestion of the meninges with several miliary hemorrhages. In the brain, particularly in the corpus striatum and especially its anterior and subependymal portion, the tuber cinereum, the cerebellum, the medulla and the internal capsule, there were noted, disposed in islets, perivascular infiltrations of two varieties, inflammatory and degenerative, with the degenerative lesions predominating. In the white matter there were also encountered some foci of cellular necrosis and other foci characterized by a disappearance of myelin and the presence of granular bodies and, sometimes, of perivascular infiltrations, surrounded by areas of hypertrophy and hyperplasia in the neuroglia. The maximum of these lesions was found in the corpus striatum, and especially in the putamen, involving the small cells. In the body of Luys many cells had disappeared; in the nuclei of the tuber and the dentate nucleus, the lesions were less numerous.

Urechia and Elekes (1925) found: "Congestion of the meninges and brain with many foci of embolic necrosis and pericapillary hemorrhage in the caudate nucleus. In many places the vessels are filled with micrococci. Most of the lesions are found in the corpus striatum and particularly in the caudate nucleus. After this and in a decreasing order: Olivary nucleus, body of Luys, and bulbar olive. In the other nuclei the lesions are slight."

These last authors quoted A. Jacob (1923), the reference for whose article could not be found, as noting: ". . . emboli with resulting necroses, in the brain,

involving particularly the putamen and the caudate nucleus." Coexistent with the necrosis, he noted in these areas a hypertrophy with proliferation of the neuroglia.

Von Lehoczky-Semmelweis (1926) reported the observations of a microscopic study of a brain made in the Neuro-Histological Institute of Professor Shaffer. These were: ". . . marked perivascular infiltration of the corpus striatum, the thalamus and the substantia nigra. The cellular elements of the infiltrate were chiefly lymphocytes, although there were also plasma cells and, in the substantia nigra, there were macrophages filled with brown pigment. A more important finding was a marked dissolution of the nerve cells in the putamen and in the globus pallidus. The process was more marked in the latter. With this condition in the putamen and in the pallidus there was a very pronounced proliferation of the glia which in part was localized and in part diffused. These partly degenerative and partly inflammatory changes can very well be rationalized with the disease process since, in the case of chorea, alterations of individual parts of the extrapyramidal systems are commonly observed. In this case the disease began during pregnancy with fever and complaint of polyarthritis. All these factors, together with the anatomic observations, support the conception that we are not here dealing with an intoxication of pregnancy, but with an infection similar to chorea in which the lesions responsible were so severe that the artificial termination of the pregnancy did not save the life of the patient."

Winkelman (1926) described the histopathology of the brain as follows: "The meninges show a relatively marked connective tissue proliferation and a slight lymphocytic infiltration which is to some extent perivascular. The structure of the cortex is everywhere disturbed. Here and there one finds certain blood vessels with a very slight perivascular infiltration of lymphocytes. The ganglion cells show mostly a moderate chromatolysis and edema. The glia cells appear to be only slightly increased in number. Preparations stained with scarlet red show only a slight content of lipoid in the ganglion cells and the walls of the blood vessels. With the low power one can see alterations in the smaller vessels and in the Nissl granules. With higher magnifications one can tell that these appearances are due not only to perivascular infiltration, but also to proliferation of the elements of the vessel wall. The endothelial cells and the adventitia cells are swollen and proliferated, resulting in a narrowing of the lumen. This narrowing is so marked that in many vessels the lumen is obliterated. The endothelial cells of the smallest capillaries are very much swollen. It can be recognized that these changes are most marked in the corpus striatum, although they are frequently noted in the cortex. The striatum appears to be unmistakably the chief site of the changes. Its normal structure has become altered. To be sure, the large ganglion cells have not diminished and are nearly normal. Many of them are surrounded by 'Trabantzellen,' which, however, is a normal finding. Others may be found with swollen, washed out protoplasm, but with no nuclear changes. On the contrary, the smaller ganglion cells show marked alteration. They are diminished in number, many are swollen with indistinct outlines, and in many the nuclei have quite disappeared. Others stain deeply and homogeneously. Small groups of glia cells can be seen where previously ganglion cells were to be found. In other respects there is not much to add to the foregoing description. The glia has markedly proliferated, which is especially to be observed in Cajal preparations. As in the cortex, the small blood vessels are easily observed on account of their thickened walls. Here and there one sees a slight perivascular infiltration of lymphocytes. Marked infiltration about the blood vessels is rare.

"The caudate nucleus shows more changes than the putamen. The glia is even more markedly proliferated, and under the ependyma of the ventricle one finds a

stretch of glia where the ganglion cells are much diminished and altered. Here and there blood vessels are visible the lymph spaces of which are enlarged by edema and filled with transudate.

"In the globus pallidus severe parenchymatous changes are missing, and in the blood vessels one sees the same changes as in the rest of the central nervous system. There are no precipitates of calcium-like material.

"Fat stains show nothing unusual either in the corpus striatum or in the globus pallidus. The iron content is apparently normal.

"The cells of the thalamus show acute changes in the Nissl granules. There is possibly some increase in the glia.. Around the third ventricle one finds small fresh hemorrhages, especially around the blood vessels. The walls of the blood vessels have here the same changes as those described. In the subthalamic region there are the same changes as in the thalamus with possibly more pronounced perivascular infiltration and more frequent hemorrhage. Around many blood vessels one sees many 'Gitterzellen' with green pigment. The substantia nigra was not to be found. The choroid plexus was normal. The pons, medulla and cerebellum showed thickening of the blood vessels and at times perivascular infiltration; apart from these they were normal. The cells of the dentate nucleus and the olive were normal. Nowhere in the central nervous system is there evidence of embolism or thrombosis."

From these histopathologic observations, the microscopic changes in the brain and meninges may be briefly summarized as follows: There is an intense congestion, not infrequently associated with petechial hemorrhage and some thrombosis. The perivascular reaction is predominately degenerative rather than inflammatory, and leukocytic infiltration is slight or entirely lacking. The neuroglia is hyperplastic, and necrobiotic changes are present in both the nerve cells and their processes. These changes reach their quantitative and qualitative maximum in the corpus striatum, especially the caudate nucleus; they are also present to a less degree in the cerebral cortex and the other nuclei of the base.

From the foregoing descriptions of the histopathology of the brain it will be seen that knowledge of this subject for chorea gravidarum is in the same state of uncertainty that obtains for Sydenham's chorea in adolescents. Marie, Boutier and Trétiakoff felt justified, on the histopathologic picture present, in differentiating their case from ordinary chorea on the one hand and epidemic encephalitis on the other. Urechia and Elekes, on quite similar findings, thought that their case lent support to those who held the two types of chorea to be identical, and they quoted Lewy as holding this view after studying the pathology of each. Sicard, as has been seen, expressed the belief that the pathologic evidence, supported by the occurrence of a parkinsonian syndrome following three cases, is sufficient to place chorea gravidarum as a manifestation of epidemic encephalitis, mainly, apparently, because he had never seen parkinsonism follow the chorea of childhood. In the one point in the cerebral pathology on which there seems to be

general agreement for both types of chorea, namely, the predilection of the lesions for the corpus striatum, the two diseases correspond exactly.

The evidence furnished by the general pathology certainly points most definitely toward an infectious origin of the condition, which, again, is in agreement with the consensus regarding Sydenham's chorea. This view of the matter is further supported by the findings with respect to the heart. An incidence of cardiac pathology, mostly acute endocarditis, of 86.9 per cent in forty-six hearts examined, certainly speaks for an infectious origin of the disease, accentuates its relation to rheumatism and, taken alone, would seem to justify the conclusion that the condition has no relation to epidemic encephalitis. It will also be observed that the pathologic evidence lends no support to the opinion that the toxemia of pregnancy stands in any etiologic relationship to chorea gravidarum.

(To be Concluded)

RED CELL REGENERATION DURING THE MENSTRUAL CYCLE *

CARL REICH, M.D.†
AND
DOROTHY GREEN ‡
NEW YORK

In the human female the process of menstruation is accompanied by a train of phenomena of which the uterine changes are only a part. Thus, pain and nervous and congestive reactions may at times become very pronounced. These various activities of the organism usually increase in intensity a few days before the menstrual flow begins, to diminish again toward the close of the period. A second lesser maximum may occur a few days after the flow has ceased. Naturally, much attention has been centered on the changes in the peripheral blood and blood-forming organs during menstruation, but the reports have been somewhat confusing. The quantity of blood lost during a normal period is also a subject of considerable discussion. Kelly [1] stated that the amount is from 60 to 240 cc.; Crossen [2] gave it as from 150 to 300 cc., and Howell,[3] from 100 to 200 cc., while Hoppe Seyler [4] was convinced that the quantity is greatly overestimated and rarely exceeds 37 cc. He arrived at this conclusion by soaking in water all the napkins used during a single period and determining the amount of hemoglobin in the solution.

The erythrocyte changes during the menstrual cycle have been studied by Detre,[5] who found an increase during the premenstrual stage, reaching the highest values just before the beginning of menstruation.

* Submitted for publication, June 24, 1931.

* From the Achelis Laboratory, Lenox Hill Hospital, Dr. G. L. Rohdenburg, director.

† Assistant bacteriologist and attending hematology clinician, Lenox Hill Hospital.

‡ Technical assistant.

1. Kelly, H. A.: Gynecology, New York, D. Appleton & Company, 1928, p. 118.

2. Crossen, H. S.: Diseases of Women, St. Louis, C. V. Mosby Company, 1930, p. 829.

3. Howell, W. H.: A Text Book of Physiology, Philadelphia, W. B. Saunders Company, 1927, p. 1004.

4. Hoppe Seyler: Ueber den Blutverlust bei der Menstruation, Ztschr. f. physiol. Chem. **42**:545, 1904.

5. Detre, L.: Ztschr. f. d. ges. exper. Med. **59**:240, 1928.

This is followed by a gradual decrease, and the lowest values are reached in the postmenstrual period. According to Pölzl,[6] there is an increase in the number of red blood cells, sometimes of from 1,000,000 to 1,500,000. This decreases with the onset of the flow. Reinert,[7] Hayem[7] and Reinl[7] agreed with these findings, as did Blumenthal[8] and Kurtschenkoff.[7] It is the opinion of Holler, Melicher and Reiter[9] that there is a hyperfunction of the bone marrow in the premenstrual phase, and that the increase in erythrocytes is an expression of this hyperfunction. Their method for determining the bone marrow function was not mentioned in the paper. Since no references to histologic studies or reticulocyte counts are made in their report, their conclusions are not determinative. These authors also found similar changes in the hemoglobin, but not as definitely as changes in the red cells. The changes in the hemoglobin seemed to follow the variations in the red blood cells. Further support of this view is voiced by Piney,[10] who stated that there seems to be no doubt that a reduction in the number of erythrocytes occurs at the time of menstruation, and this may be quite considerable in degree. Furthermore, he said that the diminution in the number of the red blood cells is definitely greater than could be explained by the menstrual loss of blood. He was not so certain that a rise in the number of red cells occurs before menstruation. In contrast, Merletti[11] found a decrease in the premenstrual erythrocyte values, and Gumprich and Davidovitsch[12] described variations in the red blood count during menstruation which were not definite.

For the present experiment, six relatively normal young women were chosen, on whom blood counts (hemoglobin and red blood cells) were done twice a week for a period of three months. The percentage of reticulocytes was also determined each time, since it is now well known that the number of reticulocytes in the peripheral blood is a reliable index of bone marrow activity. It was planned to observe the changes in the hemoglobin, red blood cells and reticulocytes over a longer time than in any of the previous reports and thus obtain a better idea of the erythrocyte changes in the blood and bone marrow coincident with the various phases of the menstrual cycle.

6. Pölzl: Wien. klin. Wchnschr. **7**:238, 1910.

7. Quoted by Gumprich, G.: Einfluss der Menstruation auf das Blutbild bei gesunden Individen, Beitr. z. Geburtsh. u. Gynäk. **19**:435, 1913-1914.

8. Blumenthal: Beitr. z. Geburtsh. u. Gynäk. **61**:614, 1908.

9. Holler, G.; Melicher, H., and Reiter, N.: Ztschr. f. klin. Med. **100**:564, 1924.

10. Piney, A.: Recent Advances in Hæmatology, Philadelphia, P. Blakiston's Son & Company, 1927, p. 180.

11. Merletti: Beitr. z. Geburtsh. u. Gynäk. **19**:459, 1914.

12. Gumprich (footnote 7).

TECHNIC

All hemoglobin determinations were made with one Sahli instrument, after standardization against the Van Slyke oxygen-combining method. Red counts were done with two standardized pipets. Separate drops from the two pipets were counted for each determination, and the results were accepted only if the counts checked within 200,000 red cells. These two counts were then averaged, and the result was taken for the final reading, thus reducing the error to about 2 per cent. Reticulocytes were counted on cover slip preparations vitally stained with brilliant cresyl blue and counterstained with Wright's stain. For each reticulocyte count, at least 10,000 red cells were examined, after the suggestion of Krumbhaar.[13] This was done by estimating the average number of red blood cells in a field and then counting by fields until the desired number had been reached. The percentage of reticulocytes was then calculated. The foregoing method gives more uniform results than the usual count of 1,000 red cells.

RESULTS

The experimental data are given in the table.

Results of Experiments

Case 1					*Case 2*				
Date	Hemoglobin, per Cent	Red Blood Cells, Millions	Reticulocytes, per Cent		Date	Hemoglobin, per Cent	Red Blood Cells, Millions	Reticulocytes, per Cent	
1/20	75	4.2	0.3		1/20	82	3.8	0.1	Menstrual
1/23	80	4.2	0.1		1/23	81	4.9	0.3	period 1/17-1/21
1/27	71	3.8	0.2		1/27	87	4.6	0.4	
1/30	74	3.9	0.3		1/30	82	4.0	0.2	
2/ 3	73	3.9	0.3		2/ 3	85	4.0	0.2	
2/ 6	78	3.9	0.1		2/ 6	84	4.4	0.2	
2/10	84	4.0	0.1	Menstrual	2/10	85	4.4	0.12	
2/13	77	4.1	0.2	period 2/11-2/16	2/13	87	4.7	0.26	
2/17	74	4.3	0.2		2/17	88	4.3	0.52	
					2/20	84	4.4	0.21	
2/20	79	3.7	0.08		2/25	93	4.3	0.22	
2/25	75	4.3	0.16		2/27	92	4.9	0.31	
2/27	80	4.9	0.11		3/3	90	4.7	0.28	
3/ 3	84	4.0	0.12						
3/ 6	84	4.2	0.09		3/ 6	93	4.8	0.29	Menstrual
3/10	93	4.6	0.08	Menstrual	3/10	89	4.3	0.4	period 3/6-3/10
3/13	76	4.2	0.1	period 3/10-3/15	3/13	89	4.7	0.13	
3/17	80	4.1	0.07		3/17	85	4.1	0.53	
					3/21	85	4.2	0.26	
3/21	85	4.3	0.09		3/25	92	4.7	0.3	
3/25	83	4.1	0.12		3/27	85	4.1	0.27	
3/27	80	4.0	0.16		3/31	91	4.4	0.15	
3/31	82	4.3	0.11						
4/ 3	86	4.5	0.04		4/ 3	80	4.4	0.35	Menstrual
4/ 7	85	4.3	0.03		4/ 7	81	4.5	0.17	period 4/2-4/9
4/10	79	4.2	0.09		4/10	95	4.2	0.14	
4/14	85	4.4	0.04	Menstrual	4/14	88	4.3	0.3	
4/17	85	4.0	0.08	period 4/14-4/19	4/17	90	4.7	0.4	
4/21	84	4.1	0.16		4/21	85	4.2	0.1	
4/24	85	4.9	0.21		4/24	84	4.3	0.25	

13. Krumbhaar: Personal communication to the authors.

Date	Hemoglobin, per Cent	Red Blood Cells, Millions	Reticulocytes, per Cent	
		Case 3		
1/20	90	5.2	0.2	
1/23	90	4.7	0.3	
1/27	93	4.2	0.4	
1/30	90	4.9	0.3	
2/ 3	95	5.0	0.2	
2/ 6	86	5.2	0.4	
2/10	88	5.0	0.3	Menstrual
2/13	90	5.1	0.2	period 2/10-2/13
2/17	100	5.0	0.23	
2/20	100	5.2	0.20	
2/25	92	5.6	0.04	
2/27	90	5.5	0.26	
3/ 3	90	5.1	0.21	
3/ 6	93	5.0	0.20	
3/10	98	5.5	0.21	Menstrual
3/13	106	5.5	0.17	period 3/10-3/13
3/17	97	5.2	0.21	
3/21	100	5.4	0.13	
3/25	92	5.2	0.17	
3/27	98	5.0	0.15	
3/31	93	5.1	0.2	
4/ 3	94	5.0	0.36	
4/ 7	93	5.1	0.10	Menstrual
4/10	90	5.4	0.24	period 4/7-4/10
4/14	90	4.9	0.14	
4/17	102	5.5	0.12	
4/21	99	5.2	0.16	
4/24	99	5.3	0.19	
		Case 5		
1/20	85	4.5	0.2	
1/23	84	4.9	0.1	
1/27	87	5.0	0.4	
1/30	90	5.4	0.2	
2/ 3	90	5.2	0.1	
2/ 6	89	5.0	0.3	
2/10	87	5.0	0.13	
2/13	82	5.0	0.25	
2/17	94	4.8	0.03	
2/20	96	5.0	0.24	
2/25	98	5.1	0.07	
2/27	95	4.8	0.28	
3/ 3	91	5.4	0.4	Menstrual
3/ 6	98	5.0	0.14	period 3/1-3/6
3/10	100	5.0	0.25	
3/13	101	5.4	0.21	
3/17	92	5.5	0.25	
3/21	95	5.5	0.24	
3/25	98	5.1	0.26	
3/27	90	5.1	0.34	
3/31	90	5.1	0.52	
4/ 3	88	5.6	0.26	Menstrual
4/ 7	87	4.8	0.25	period 4/2-4/7
4/10	86	4.6	0.19	
4/14	96	4.9	0.13	
4/17	92	5.0	0.29	
4/21	89	4.7	0.26	
4/24	90	4.5	0.15	

Date	Hemoglobin, per Cent	Red Blood Cells, Millions	Reticulocytes, per Cent	
		Case 4		
1/20	78	4.7	0.1	Menstrual
1/23	80	4.9	0.2	period 1/20-1/25
1/27	77	4.3	0.1	
1/30	78	4.6	0.2	
2/ 3	88	5.4	0.3	
2/ 6	80	4.7	0.1	
2/10	90	5.1	0.08	
2/13	83	4.8	0.11	Menstrual
2/17	90	4.7	0.19	period 2/13-2/18
2/20	92	4.7	0.13	
2/25	92	5.3	0.11	
2/27	90	4.9	0.09	
3/ 3	96	4.8	0.20	
3/ 6	88	5.1	0.08	
3/10	91	5.0	0.06	Menstrual
3/13	86	4.8	0.06	period 3/12-3/17
3/17	90	4.8	0.18	
3/21	87	4.6	0.12	
3/25	94	4.8	0.22	
3/27	90	4.5	0.06	
3/31	92	5.1	0.13	
4/ 3	87	4.8	0.22	
4/ 7	83	4.8	0.10	Menstrual
4/10	94	5.5	0.09	period 4/8-4/13
4/14	90	4.9	0.14	
4/17	90	4.5	0.39	
4/21	87	4.7	0.11	
4/24	92	5.0	0.18	
		Case 6		
1/20	89	4.4	0.1	
1/23	89	5.0	0.09	
1/27	75	4.3	0.10	
1/30	82	4.8	0.20	
2/ 3	82	4.7	0.1	
2/ 6	82	4.2	0.2	
2/10	85	4.4	0.18	
2/13	91	4.7	0.08	
2/17	86	4.8	0.07	Menstrual
2/20	91	4.7	0.02	period 2/19-2/23
2/25	83	4.3	0.03	
2/27	85	5.1	0.09	
3/ 3	80	4.3	0.2	
3/ 6	80	4.2	0.08	
3/10	89	4.8	0.09	
3/13	76	4.5	0.09	Menstrual
3/17	91	4.6	0.06	period 3/13-3/17
3/21	80	4.5	0.12	
3/25	84	4.6	0.12	
3/27	84	4.8	0.12	
3/31	85	4.7	0.08	
4/ 3	90	4.6	0.13	
4/ 7	88	4.5	0.12	Menstrual
4/10	92	5.0	0.15	period 4/7-4/11
4/14	85	4.3	0.16	
4/17	90	4.5	0.08	
4/21	84	4.7	0.18	
4/24	90	4.7	0.26	

COMMENT

From a study of the data presented, it is understood why the reports in the literature are so confusing. The results are far from consistent, and there are no definite variations in the hemoglobin and red blood cells associated with menstruation. The coincident changes in the reticulocyte percentage support this statement. If there were a regular and significant drop in the red count during menstruation, there should have been a definite postmenstrual reticulocyte peak, indicating regenerative activity in the bone marrow. No such peak occurs, and the percentage of reticulocytes varies during the different phases of the menstrual cycle merely within the limits of error of the method. This indicates that the bone marrow is not called on to increase its regenerative activity. It therefore appears that in normal women the process of red cell regeneration is but slightly, if at all, influenced by the menstrual cycle.

SUMMARY

1. The process of red cell regeneration was studied in six relatively normal young women in relation to the menstrual cycle.

2. Studies of the hemoglobin and red blood cell counts made at biweekly intervals over a period of three months reveal no definite changes coincident with the various phases of menstruation.

3. The activity of the bone marrow as indicated by the reticulocyte count is not influenced by the menstrual cycle.

Book Reviews

Handbuch der inneren Medizin. Herausgegeben von G. von Bergmann und R. Staehelin. Band VI. Nieren und Ableitende Harnwege: Die doppelseitigen hämatogenen Nierenerkranungen, von F. Volhard. Die ein-und beidseitig auftretenden Nierenkrankheiten (sogenannten chirurgische nierenaffektionen). Blase, Prostata, Hoden und Nebenhoden, Samenblasen, funktionelle Sexualstörungen, von F. Suter. Second edition. Price: Teil 1, 98 marks; Teil 2, 99.60 marks. Pp. 2137, with 298 illustrations. Berlin: Julius Springer, 1931.

The remarkable growth in the last two decades of the body of knowledge concerning Bright's disease is directly reflected in the evolution of the second edition of Volhard's great classic. From 673 pages of text in the 1918 volume, 1,722 pages, many in small type, have developed. A bibliography of about 20 pages in 1918 has increased to 152 pages in 1931. The literature is so thoroughly reviewed by extensive quotations and abstracts that an entire library is represented in these two books. Nothing of any significance has been left out. Add to this thoroughness a lucid, direct and pleasing style, perfect arrangement of the material, good typography and numerous excellent illustrations, and one has a permanent literary monument to Volhard's genius.

No attempt will be made to review more than a few aspects of the scientific contents, although every page is replete with interesting material. Volhard is a more confirmed "vital secretionist" than ever before, in spite of the recent work of Richards and his associates. He doubts the existence of glomerular filtration and even denies the occurrence of filtration in the choroid plexus. At times he allows the warm conviction of beautiful logic to overweigh the cold evidence of facts. He attacks Cushny's theory of urine formation on grounds somewhat antiquated at present. His arguments are always stimulating, however, and should provoke further investigation. There is an excellent discussion of the nerve supply of the kidney and of the problems of nervous regulation of renal function. The American work on renal function tests by Addis and Van Slyke and their associates is well presented. The author indulges in some clever juggling of Ambard's formulas to arrive at conclusions of rather doubtful objective value.

As to lymph formation and edema in general, Volhard vigorously supports the theory of active secretion by the vascular and lymphatic endothelium. In fact, his credo is that the function of the capillaries is to regulate and inhibit mechanical filtration. Edema, therefore, is caused largely by increased permeability of the capillary wall on the basis of general damage of the tissues, a vague "dropsy of the tissue colloids." Renal edema is always extrarenal in origin; acute nephritic edema is cardiovascular, while chronic nephrotic edema is definitely attributed to albuminuria and hypalbuminemia, in view of the recent clinical and experimental data on this relationship.

It is to the problem of hypertension that Volhard has made his most important contributions. The "red" and "pale" types are distinguished on the basis of the mechanisms involved in their production. In the "pale" hypertensives (acute diffuse glomerulonephritis, "malignant" hypertension, eclampsia) there is a general arterial spasm (also angiospastic neuroretinitis) due to the presence in the blood serum of directly pressor chemicals and substances that sensitize the arterioles to the normal epinephrine content of the blood. These substances perhaps originate in the kidney under conditions of local circulatory or metabolic derangement. The evidence for all this seems quite acceptable to Volhard. Confirmation of the facts is urgently indicated. As to "red" hypertension, the only unquestionable etiologic factor is age. The author's attempt to explain essential hypertension on unproved physical changes in the small arteries will probably not satisfy most investigators in this field, but the distinction made between active contraction of arterioles and passive resistance to distention may represent a germ of the truth. One thing is certain, as Volhard states: Every persistent hypertension is in close relation

to the kidney, being either the result or the cause of a renal disease. The cerebral vascular disturbances so common in hypertension are dealt with along the lines of recent work on functional vascular disease. Albuminuric retinitis is termed "angiospastic retinitis" and correlated with the chemical pressor agents responsible for hypertension.

After an excellent historical review, Volhard dismisses physiologic, symptomatic and histologic classifications of renal disease and makes a powerful plea for the now famous "pathogenetic system." Opposing points of view are freely discussed, at times in a charmingly personal vein. How "ischemia" and "angiospasm" displaced "inflammation" in Volhard's thoughts on glomerulonephritis and the "combination form" ("malignant nephrosclerosis") is dramatically portrayed in this and in later sections of the text. The author naively laments the original lack of interest in his "discovery" on the part of prominent pathologists and clinicians. Recently, however, there has been adequate recognition. Whether Volhard is right or wrong, his point of view on the histogenesis of glomerular and vascular lesions has been a potent ferment and will continue to stimulate inquiry into fundamental problems of the pathologic physiology of the vascular system.

In the second volume, the clinical aspects of Bright's diseases are thoroughly covered, numerous and detailed case reports being included. Chronic nephrosis is not considered as a primary metabolic disease, but the whole nephrotic syndrome is attributed to loss of normal serum protein in the urine. As to why slight glomerular changes are associated with most severe albuminuria, is a mystery. Volhard says decisively: "Genug, das Nephritis-Nephrose-Problem is heute ungeklärter denn je" (Amen). A systolic blood pressure level above 120 mm. of mercury always rules out pure nephrosis, but a lower figure does not justify a diagnosis of "nephrosis," because patients with proved diffuse glomerulonephritis may have low blood pressures for a long time. In short and in truth, "die Diagnose einer echten Lipoidnephrose" is also "keine leichte Aufgabe."

Volhard does not believe that a true diffuse nephritis has ever been produced in animals. The essence of chronic nephritis is seen in the persistence or occurrence of general and renal vasoconstriction. The varying clinical forms of the disease depend on the balance between circulatory disturbance and restitution. Even in chronic nephritis there is a long period of functional vascular trouble. As to treatment, von Noorden's advice to the physician is given: Forbid as little, instead of as much, as possible. Allen's rigid salt-free diet is enthusiastically recommended for patients with hypertension. Volhard is skeptical about the effects of most of the so-called vasodilators. His clinical subdivision of hypertension is rather complex and confusing, but the author makes a heroic attempt to mix functional and organic renal vascular changes in the proper proportions to explain various difficult problems.

The arrangement of the subject matter in the part by Suter follows the plan of the first edition. There are general sections that deal briefly with the symptomatology and methods of diagnosis of urological conditions. The special sections take up systematically the congenital malformations of the urinary tract, the various infections, calculous disease, obstructive syndromes, tumors, cystic conditions, inflammations of the perirenal fat, renal vascular accidents, diseases of the bladder, prostate, testes and seminal vesicles and functional disturbances of the male genital organs. The recent advances in the diagnosis and treatment for surgical diseases of the urinary tract are well covered in this edition. The author presents conflicting theories and practices in an objective manner. The illustrations are well chosen, and the bibliography is satisfactory. This section of the "Handbuch" should prove to be a valuable source of reference to both urologists and internists. It must be pointed out, however, that details of surgical technic do not come within the province of the text.